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This pellagra commission has issued two series of papers, the first series¹ dealing with certain phases of the work up to the end of 1912 and the second series² dealing with the investigations up to the end of 1913. The results and the conclusions of this earlier work have been confirmed and amplified by the subsequent investigations. Some of the results are merely confirmatory of facts already well known concerning pellagra; others are somewhat at variance with previously recognized conceptions and old theories of the etiology of pellagra, including the ancient theory of dietary deficiency, again exploited by Sandwith³ and others in the recent literature. It is our purpose to present in this third report those portions of our recorded observations which seem to have the most important bearing upon the unsettled problems of pellagra.

Inasmuch as the various members of the commission have been taken away from the work, it seems very probable that the present series of papers will represent the final report to be made by the commission as originally constituted. It is hoped, however, that the inves-

1. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Pellagra—A Summary of the First Progress Report of the Thompson-McFadden Pellagra Commission, *Jour. Am. Med. Assn.*, Jan. 3, 1914, lxii, 8; Siler, J. F., and Garrison, P. E.: An Intensive Study of the Epidemiology of Pellagra: Report of Progress, *Am. Jour. Med. Sc.*, 1913, cxlvi, 42, 238; Jennings, A. H., and King, W. V.: An Intensive Study of Insects as a Possible Etiologic Factor in Pellagra, *Ibid.*, 1913, cxlvi, 411; Myers, V. C., and Fine, M. S.: Metabolism in Pellagra, *Ibid.*, 1913, cxlv, 705; Hillman, O. S.: Some Hematological Findings in Pellagra *Ibid.*, 1913, cxlv, 507; MacNeal, W. J.: Observations on the Intestinal Bacteria in Pellagra, *Ibid.*, 1913, cxlv, 801. This entire series of papers, together with a Table of Contents, is included in *Pellagra—First Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School and Hospital, New York, 1914*, pp. iv + 148.

2. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Further Studies of the Thompson-McFadden Pellagra Commission—A Summary of the Second Progress Report, *Jour. Am. Med. Assn.*, 1914, lxiii, 1090; Introduction to the Second Progress Report of the Thompson-McFadden Pellagra Commission, *ARCH. INT. MED.*, 1914, xiv, 289; A Statistical Study of the Relation of Pellagra to Use of Certain Foods and to Location of Domicile in Six Selected Industrial Communities, *Ibid.*, 1914, xiv, 292; The Relation of Methods of Disposal of Sewage to the Spread of Pellagra, *Ibid.*, 1914, xiv, 453; Hillman, Oliver S., and Schule, Paul A.: Further Observations on the Blood Count in Pellagra, *Ibid.*, 1915, xv, 147; Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Statistics of Pellagra in Spartanburg County, S. C., Including Geographical Distribution of the Disease and Its Relation to Race, Age, Sex and Occupation, *Ibid.*, 1915, xv, 98; Singer, H. Douglas: Mental and Nervous Disorders Associated with Pellagra, *Ibid.*, 1915, xv, 121. This entire series of papers, together with a Table of Contents, is included in *Pellagra II—Second Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School and Hospital, New York, 1915*, pp. iv + 169.

3. Sandwith, F. M.: Can Pellagra Be a Disease Due to Deficiency in Nutrition? *Tr. Nat. Assn. for Study of Pellagra*, 1912, ii, 97; Is Pellagra a Disease Due to Deficiency of Nutrition? *Tr. Soc. Trop. Med. and Hyg.*, 1913, vi, 143.

tigation of pellagra thus begun under the auspices of the New York Post-Graduate Medical School and Hospital will be continued under the same or under other auspices until the numerous theories concerning the nature of this disease shall have been completely overshadowed by scientifically demonstrated facts.

The series of papers, constituting the third report, includes the important contributions of some of those scientists who have collaborated with our commission by undertaking the study of pellagra from particular individual points of view. We consider ourselves especially fortunate to have had the collaboration of these investigators and are very grateful to them for the papers which they have written for this report. Needless to say, these collaborators are alone responsible for their interpretations and conclusions, and they alone deserve the credit for the results which they report. It is a special pleasure to acknowledge our obligation to Dr. C. B. Davenport, to Dr. Elizabeth Muncey and to Dr. E. B. Vedder, Capt. Med. Corps, U. S. A., for their studies of heredity and dietary deficiency in pellagra. We wish also to give credit for faithful technical assistance to Dr. F. L. Letts and to Mr. Sam Goldin.

THE HEREDITARY FACTOR IN PELLAGRA*

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I. STATEMENT OF THE PROBLEM

In certain parts of our country, and above all in our southern states, there are occasionally seen persons whose hands, feet and even other parts of the body show chronic, symmetrically placed,¹ eczema-like rough patches or a formation of bullae and desquamation over larger or smaller areas. A condition of dermatitis may be due to a number of causes; to tuberculosis, to a filamentous fungus, to poisoning from without or within. Particularly the poison that can be expressed from certain mucors will, when injected into the veins of a rabbit, cause extensive desquamation of a similar sort. But in certain of these persons there is, in addition to the chronic desquamation, a persistent diarrhea or dysentery.² In consequence of a disturbing factor, probably a tissue poison, of whose presence these are merely indications, the affected person is liable to die; or else he recovers as the cooler weather comes on, to relapse into the same condition the following spring; or perhaps he recovers permanently. Now, these two states, skin inflammation and diarrhea, may occur independently of each other, but when they occur together the diagnosis of pellagra is nowadays rendered. If in addition to these two symptoms an individual shows an unwonted nervous or mental state, whether unusually excited or unusually depressed or confused and demented, then the diagnosis of pellagra is given with greater confidence.

Now, is this association of traits a necessary one, due to a single cause, for example, the introduction of a specific poison of parasitic or other origin, or is it an accidental association; just as one will find blondness, hair curliness and short stature combined in a certain proportion of the population? If an anthropologist should describe this type and give it a name, then observers would easily detect persons belonging to this type and the type would then begin to exist.

* Submitted for publication March 9, 1916.

* From the Eugenic Record Office, at Cold Spring Harbor, Long Island, N. Y. This paper forms a part of the third report of the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

1. "Symmetry of dermal lesions is a widespread phenomenon. Thus in leprosy the eruption is frequently symmetrical, remarkably so, but this is by no means a constant feature."—Cantlie, J.: *Allchin's Manual of Medicine*. I, p. 239.

2. Persistent diarrhea accompanies skin diseases of other types. This is so in leprosy.

It would not have existed before because there cannot be a type without a definition and a name. I do not wish to assume the rôle of an iconoclast, yet I cannot but be impressed by the difficulties that are met with in the diagnosis of pellagra. These difficulties led Lavinder³ to say: "It is possible, of course, but rather unlikely, that more than one morbid entity may at present be included under pellagra." And the same author tells of a French school which speaks of the pellagrous syndrome. Also Lombroso said: "There is no disease; only the diseased." It is generally held that the erythema or dermatitis is the essential characteristic of the disease. But some Italian authors speak of pellagra sine pellagra, meaning that skin lesions are absent. The nervous and mental symptoms are not found in most cases. "In Italy it has been variously estimated that from 4 to 10 per cent. of pellagrins are insane."³ Grimm⁴ states that "In this country about 7 per cent. of the pellagrous whites are insane." And Singer⁵ finds that, in 1912, 6.2 per 10,000 pellagrins from Spartanburg County were committed as insane.

II. HYPOTHESIS

To make progress in the inquiry concerning a possible hereditary factor in so ill-defined and variable a disease as pellagra, it is first of all necessary to select some hypothesis, based upon the best available knowledge, to see if it will work. Preliminary studies show at once that pellagra is not inherited like eye color; if there is any factor of heredity at all it must be largely obscured by numerous other factors.

To the best of our knowledge, pellagra is the reaction of the individual to the poisons elaborated in the body, probably by a parasitic organism. This accords with the conclusion of Siler, Garrison and MacNeal,⁶ that pellagra is in all probability a specific infectious disease communicable from person to person. These poisons cause, or tend to cause, inflammations and frequently tissue necrosis in the highly vascular layers that lie below epithelial surfaces, such as the skin, the

3. Lavinder, C. H.: Pellagra, A. Précis, Pub. Health Bull., 1912, No. 48, Ed. 2, pp. 29, 30.

4. Grimm, R. M.: Pellagra: A Report on Its Epidemiology, Pub. Health Rep., March, 1913, No. 120, pp. 5, 8.

5. Singer, H. D.: Mental and Nervous Disorders Associated with Pellagra. *THE ARCHIVES INT. MED.*, xv, 121, 149.

6. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Pellagra: A Summary of the First Progress Report of the Thompson-McFadden Pellagra Commission, *Jour. Am. Med. Assn.*, 1914, lxii, 8; Introduction to the Second Progress Report of the Thompson-McFadden Pellagra Commission, *THE ARCHIVES INT. MED.*, 1914, xiv, 289; Further Studies of the Thompson-McFadden Pellagra Commission; a Summary of the Second Progress Report, *Jour. Am. Med. Assn.*, 1914, lxiii, 1090.

lining of the mouth, stomach and intestine. The inflammations are most destructive in individuals that are least fitted to resist their untoward effects or provide a self-regulation. It is probable that the inflammation of the skin, lining of the mouth and various portions of the gut are incited by the same irritant; for such an association is found in some other diseases, for example, leprosy. Thus the external and the internal inflammations may be regarded as fundamentally one and the same symptom.

Further, in persons so disposed, the toxin of the disease may disturb the harmonious adjustment and coordinate working of the elements of the central nervous system, resulting, in different individuals or at different times, in underinhibition or overinhibition, in mental confusion, disorientation and other symptoms. Nervous and mental troubles are found in other diseases in which dermatitis is a symptom, for example, in leprosy, in which neuritis, and eventually neuralgia, are usual; also, in typhoid fever depression and confusion are common.

The nervous changes in pellagrins have been studied by Dunlap,⁷ who finds in the motor areas of the brain a swelling of the nerve cells and a heavy pigmentation. These changes are identical with those described under the term "central neuritis;" they are found also in cases of Korsakoff syndrome, and in chronic alcoholism. A similar swelling of nerve cells has been seen in the spinal cord in cases of beriberi. There is, therefore, no specific nervous change characteristic of pellagra, but only a change which it shares with other conditions of nerve irritation, in some cases, as in alcoholism, clearly associated with poisoning.

As this paper was about to be sent to the printer there came to my hand the second report of the pellagra commission, containing Singer's paper. Singer concludes that "pellagra is especially frequent in individuals of faulty nervous organization and in consequence there occurs, in association with it, a greater percentage of such disorders as dementia praecox, manic-depressive insanity, hysteria, etc., than prevails among healthy persons, yet the vast majority of the mental disturbances occurring in connection with pellagra are of no more significance *qua* 'insanity' than are the deliriums of typhoid fever." That there should be a correlation between mental insufficiency and pellagra is not strange, since the mentally insufficient are, on the whole, less likely to appreciate the importance of sanitary surroundings and less able to avail themselves of them, and the reports of the pellagra commission prove the close relation of pellagra to poor sanitation. No doubt, also, persons who are mentally well developed are, on the whole, more likely to care for their bodies and keep themselves in good condition than are

7. Dunlap, Charles B.: The Pathological Changes in the Nervous System in Pellagra, New York State Bull., February, 1915.

the mentally deficient or unstable. Other things being equal, pellagra is more liable to make headway in "Nam Hollow"⁸ than in the cottages on the cliffs at Newport.

Our hypothesis is that in the pellagra reaction there is a hereditary factor. This hypothesis is supported by certain general and by certain specific considerations. Generally, we may say that any disease, simple or compound, is known by its symptoms. Now symptoms of disease are the behavior or reaction of the organism, its organs and tissues, to the presence of certain specific stimuli or irritants that are abnormal to the body. What the reaction shall be depends not only upon the nature of the specific stimulant, but also upon the specific nature of the reacting organism or part. And if there is one thing of which experience perfectly assures us it is that different individuals react dissimilarly to the same stimulus. Such dissimilarity of reaction is conditioned both by fundamental dissimilarity in the constitution of the organism and by dissimilarity in antecedent experiences of the organism; but the latter, in turn, is conditioned in part by the former; so that the fundamental dissimilarity of the constitution of the organism must be held to be the principal cause of the diversity which persons show in their reaction to the same disease-inciting factors.

This constitution of the organism is a racial, that is, hereditary, factor. And if it appears that certain races or blood lines react in the pellagra families in a specific and differential fashion, that will go far to prove the presence of a hereditary factor in pellagra. A superficial consideration of the epidemiology of pellagra suggests that colored persons, who differ from most white people in having more or less negro blood, are less subject on the whole to the disease than white persons. Thus Siler and Garrison⁹ in their early studies found pellagra nearly five times as prevalent among all white people as among negroes, or, exclusive of the cotton mill villages, two and one-half times as prevalent among the white population as among negroes. If the sanitary conditions of the white people were much inferior to those of the negroes the difference of incidence might be explained as due to such conditions, but this seems not to be the case. Siler and Garrison state that on inquiring of physicians, "without exception we were informed that pellagra in negroes was of comparatively infrequent occurrence." In the same tenor Grimm⁴ states: "In the districts which I visited pellagra seemed to spare the negro to a remarkable extent, and it was not unusual to find a physician who, although he had seen many cases of

8. Eugenics Record Office, Memoir No. 2.

9. Siler, J. F., and Garrison, P. E.: *An Intensive Study of the Epidemiology of Pellagra*; Report of Progress. *Am. Jour. Med. Sc.*, 1913, cxlvi, 42, 238; also reprinted in *Pellagra: First Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate School and Hospital*.

pellagra among the whites, had never seen one among the blacks." But the proportion of pellagrins who die or go insane is stated by him to be larger among the negroes than among the white population. We have thus here apparently strong evidence of a racial difference, and that is synonymous with a hereditary difference. However, in 1915, Siler, Garrison and MacNeal,¹⁰ while confirming their earlier statistics that for Spartanburg County "the disease was about three times more prevalent in the white population as a whole than in the negroes," conclude, "we are inclined to believe that negroes as a race are only slightly, if at all, less susceptible to pellagra than the white population."

In view of the dependence of pellagra on industrial conditions and sanitation and the difference in these respects between the white and the negro population in different counties and states; and in view of the fact that all grades of hybrids between white and negro are grouped as colored, or negro, it is difficult to draw correct inferences as to susceptibility from the apparent difference in morbidity between the negro and the white population.

A consideration of the question whether even inside of the group of white persons hereditary strains differing in their reaction to the cause of pellagra are to be found must be deferred until we have further analyzed the nature of pellagra. The considerations already presented justify, I think, the hypothesis that there is in pellagra a hereditary factor.

To summarize: "Pellagra" is a term applied to inflammations and ulcerations of the musculo-vascular layer of the skin and intestine, doubtless due to the presence of a toxic agent which also induces in predisposed persons nervous and mental disturbances. The differences in the degree of expression of these symptoms are due, among other things, to differences in the hereditary constitution of the affected individuals, and variation in the symptom complex is due to variations in the constitutional, or hereditary, susceptibility or resistance of the different organs affected by the toxin.

III. TEST OF THE HYPOTHESIS

In the first report of the Thompson-McFadden Pellagra Commission⁶ there were found for the different townships of Spartanburg County, population 83,000, proportions of pellagrins varying from 0 to 71 per 10,000. In the city of Spartanburg, with a population of 17,500, eighty-five cases were described, or forty-nine per 10,000, or less than

10. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Statistics of Pellagra in Spartanburg County, S. C., including Geographical Distribution of the Disease and Its Relation to Race, Age, Sex and Occupation, *THE ARCHIVES INT. MED.*, 1915, xv, 98.

one-half of 1 per cent. If now in many families more than one case is found in a family of under twenty-five or even fifty persons, the chances are large that the association is not an accidental one. As a matter of fact, out of 142 families reported on by Dr. Muncey, thirty-seven, or nearly one fourth had more than one case of pellagra. Actually, families with five cases are not uncommon, being nine out of thirty-seven, and even families with eight and nine to the family of close blood relations are known. This high incidence of pellagrous symptoms among blood relatives may be due to contamination through association, or it may be due to constitutional similarity, such that when one member of a family is liable to the disease others are liable also. I think the evidence shows that both possibilities are realized. The evidence for contamination is strong, but the evidence for constitutional diversity is not less strong.

1. EVIDENCE FOR THE COMMUNICABILITY OF PELLAGRA

That infection plays a rôle in the spread of pellagra can, I think, hardly be doubted. The case of mating A (Fig. 15), is especially suggestive. At a time when pellagra was almost unknown in Spartanburg County, a married woman was associated in her work with Italian immigrants during one summer. The next spring she had the typical symptoms of pellagra and died of pellagra in a few months. This was in 1894. In 1899 the mother of this woman first showed signs of pellagra; she lingered along, showing marked mental symptoms, until 1903. Her husband, father of the propositus, revealed symptoms of pellagra the year his wife died; he failed mentally and died in 1910. Meanwhile, one of his older daughters was stricken with the disease in a severe form, was nursed by various friends and neighbors, and finally died in 1910; and many new cases of pellagra broke out in the mill village the next year. A 5-year-old daughter of the last-named victim died from pellagra the same year (1910) as her mother, and the next year another daughter was stricken, but still resists death. Certainly this looks like communication.

Other cases of possible communication were collected by Dr. Muncey. Thus, in the progeny of mating C (Fig. 38), a girl first showed the disease in the spring of 1908 and it affected especially the skin of the feet and legs. Her father dressed her desquamating and raw skin and he came down with the disease in the spring of 1909 and died of it in June, 1910. Again, in mating 10 B, we have the history of a father in whom pellagra appeared in 1911 with severe dermal symptoms and these have recurred every spring since. His ten-year-old son sleeps with him, and in July, 1914, he developed severe erythema with slight intestinal disturbance.

Again, mothers are more intimately associated with children than are fathers. Correspondingly, we find 57 cases of mother and child, both pellagrous, and only 17 of father and child. But mothers are 2.3 times as apt to be pellagrous as fathers. Multiplying 17 by 2.3 we get 39, the theoretical number of children to contrast with the 57 pellagrous children of affected mothers. And the difference between these two numbers roughly corresponds with that of paternal and maternal contact. This, again, speaks for communication.

An examination of the pedigrees shows a large number of cases in which both parents are affected, and one seems to have become infected by the other. I give some cases:

CASE C (Fig. 12).—The father of a family which lived next door to a pella-grin developed a well-marked case of pellagra in April, 1911; a son showed the same symptoms in the same month and the mother in June of the same year.

CASE B (Fig. 11).—Father and mother showed the disease at about the same date.

CASE B (Fig. 9).—The father died of pellagra in 1909; the mother came down with it in June, 1912.

CASE C (Fig. 35).—The mother had typhoid fever in 1892 and dysentery for several years following in the summer. In May, 1912, typical symptoms of pellagra appeared, and in the same month they appeared in her husband, who was tubercular and very weak.

CASE A (Fig. 15).—This is the case of a man and wife whose daughter worked with Italians and contracted the disease in 1894. The mother first showed pellagra in 1899; she died of it in 1903 and her husband contracted pellagra in the same year, dying of it in 1910. A daughter of this pair died in 1910 of pellagra and her husband not long after had typhoid, followed by eczema.

Of the following cases no figures were made for this paper. The references at the end are to the families fully described in the paper of Dr. Muncey, which follows this:

CASE A, C.—A man living in the endemic area developed pellagra in the spring of 1909 and died of it in August. His wife, who cared for him until he went to the hospital, had an attack the next spring, and this recurred (S. B. family).

CASE B, B.—A man developed pellagra in 1911 and this has recurred each spring since. His wife had a severe attack in 1914 (T. family).

CASE C, B.—A widower showed pellagrous symptoms in 1909 and was nursed by his daughter; she had good health until pellagra set in in 1911, and her husband developed the disease in 1912 (B. S. family).

CASE D, B.—A woman had a severe attack of pellagra in the autumn of 1909 and died of it in April, 1910. Her husband had pellagrous symptoms in 1910 and these have recurred annually since (S. family).

CASE E, A.—A housewife developed pellagra in May or June, 1911, and died of it in November, 1912. Her husband, generally of good health, developed typical symptoms of pellagra in November, 1912, and these recurred in 1913 (B. R. family).

Thus, in a marked proportion of matings husband and wife developed the disease in such time relations as to make it probable that the

disease was communicated from one to the other. In these cases there was no close blood relationship between the consorts. The cumulative evidence of communication seems irresistible, and such communication may be readily admitted.

2. EVIDENCE OF CONSTITUTIONAL SUSCEPTIBILITY TO PELLAGRA

The fact that pellagara is communicable does not, however, render the existence of a hereditary factor less probable. For it is not the parasite that causes the disease; the symptoms of the disease are the way the organism reacts to the parasite and it is clear that the organism has as much to do with this result as the parasite. And just as we find certain children who are exposed catching the disease, so we find others, equally exposed, going scot free. Thus from mating F, B are derived four children of whom three came down with pellagra, but the fourth, living in the same house as the others, has not had it. Again, from mating C (Fig. 12) came four children, of whom three were attacked, while one, the oldest girl, has never shown any symptoms of pellagra. In mating A (Fig. 28) there is a daughter who had erythema and intestinal symptoms for three years, yet her sister, who slept in the same bed, has not contracted the disease. On the theory of an intermediary host and a carrier of the disease this is explicable, but the chance of the sister not becoming inoculated is so small that it seems more probable that she resisted infection by virtue of a hereditary capacity.

Moreover, the one thing which seems overwhelmingly to demonstrate an inheritable factor to pellagra is the difference in the course of the disease in different families. In the related matings A and B (Fig. 28), in which none of the parents are affected, we see that the symptoms of the disease are quite mild. The parents in C, B both have had the disease, but in slight form. Of their ten children, only one showed symptoms and these have recurred through three years, but they are not severe. Contrast such families with A (Fig. 15), in which father, mother and three daughters, out of nine children, have died of the disease, and of two affected children of one of them, one died at about the time her mother died with symptoms much like those of pellagra, and the other has the disease in a severe form. It is true that the difference in the course of the disease may be accounted for by a difference in the virulence of the hypothetical specific organism that induces the symptoms, but pathogenic organisms are not the only ones that vary in their qualities, and variations in resistance to disease in the higher animals is as well established a fact as variations of virulence of parasitic microorganisms.

3. BIOTYPES IN REACTION TO PELLAGRA TOXIN

We have seen reason for believing that the inflammations and histolysis of the derma and of the musculovascular coat of the intestine are due to one cause, a toxin that is developed during the attack. Nevertheless, there is in different individuals a striking difference in the reactions of skin, mouth and intestine. Also, the mental symptoms vary greatly in intensity in different persons. It follows from all this that, as we have indeed already seen, the symptom complex shown by different individuals is very varied. We have now to inquire whether this variation occurs at haphazard in the pellagrous population, or whether a particular type of symptom complex tends to run in one family and another type in another family. In biological language, are there strains, or biotypes, that differ in the relative susceptibility, or resistance, of the various organs to the pellagrous toxin?

To get an answer to this inquiry I have gone through the thirty-seven family histories secured by Dr. Muncey in which there is more than one affected person, and looked for families in which there is an exceptionally high or low incidence among pellagrins of a particular symptom. Such families appear at once. Thus, none of the affected individuals of the following families show any of the mental symptoms, such as overactivity, violence, depression, immobility, delirium, which are found in about 10 per cent. of pellagrins generally. From mating C (Fig. 37) there were three affected individuals; in C (Fig. 38) father, two daughters, and their first cousin were affected; in A (Fig. 36), the mother, two children and one grandchild had the disease; in C (Fig. 35), both parents and one child; in B (Fig. 9), both parents and their only child; in B (Fig. 11), father and two children; in C (Fig. 12), both parents and three children; in Fig. 32, two; in B (Fig. 33), mother and all three children; in B (Fig. 29), mother and four children; in D (Fig. 30), mother and daughter; in C (Fig. 31), grandmother, mother and two sons; in B (Fig. 23), mother and two children; in F family, mother and four children; in B (Fig. 8), mother and all four children affected; in family shown in Figure 28, two sisters and their first cousin; in A (Fig. 10), mother and child. It is thus easy to find fairly large sections of affected families in which none of the individuals show mental symptoms. In the following families mental symptoms are more common. In A (Fig. 15) the pellagrous father showed eventual complete mental failure. The mother was feeble-minded and mental symptoms were pronounced three months before her death with pellagra. She has a daughter who has no skin trouble, but is feeble-minded and suicidal at times, and another daughter is a pellagrin, who, in turn, had a daughter that had severe mental trouble accompanying bowel trouble, and another who died "crazy" at five

years, with erythema and bowel trouble. Thus mental trouble appears in five members of this little group.

Again in A (Fig. 16) the father has recurrent spring attacks of stomatitis, bowel trouble and eruptions on hands and face accompanied by mental symptoms. His son had bowel and stomach trouble with erythema for three years and was insane for a year before he died.

Again, in B (Fig. 25) two sisters had each indigestion followed by bowel trouble, eventually erythema and then marked mental symptoms. In A (Fig. 6) two daughters have dermal and intestinal trouble and also marked mental failure and one grandnephew has nervous symptoms in addition to the erythema. In B (Fig. 7) the mother was already in a hospital for the insane before the physical symptoms appeared. Her father had committed suicide and her mother's brother was a manic-depressive.

More rarely single families will show a marked prevalence of intestinal symptoms with or without eruptions. Thus, in A (Fig. 20) the father died of chronic bowel trouble; his daughter died of "tuberculosis of the bowels, probably pellagrous"; she married a man who had intestinal disorder, probably with skin eruptions, whose father had chronic bowel trouble; two of their three children had "typhoid," so-called, with symptoms like pellagra in one case at least; one died and one recovered. Here are six sufferers from chronic intestinal disorders, only one of whom is typically pellagrous. In a second case the grandfather died of "typhoid fever." Of his four children, one died at 41 of chronic bowel trouble and had (C, Fig. 14) a daughter who had "typhoid" and later eruptions and dysentery; two of her sibs were typical pellagrins. Another one of the grandfather's sons had typhoid in 1869 and in 1913 intestinal and dermal disorders. Here we have four cases of typhoid and bowel trouble without dermal ulcers. In T. F. family the father had typical pellagra and so has one of the children, but one other child died of typhoid and one at 4 years of bowel trouble. The father in mating B (Fig. 19) died of typhoid fever (1895) and so did his brother, who had long been a victim of chronic bowel trouble. The daughter of this mating had pellagra, and of her children, one died in infancy of stomach trouble and "thrush," stomatitis, and another died in infancy of cholera infantum, infantile diarrhea. Thus, in four out of five intestinal trouble only is marked. Of mating B (Fig. 21), the mother of a pellagrin had typhoid and so had her brother, their mother's sister and mother's parents. Other cases might be cited.

Finally, certain strains are characterized by skin troubles chiefly. Thus, in the family represented in Figure 18 the earlier ancestor is characterized by eczema with some indigestion; his two children had eczema, one so severely that her hand had to be wrapped in winter:

a daughter of the latter had eczema all her life. In the family shown in E (Fig. 26) the mother had stomatitis May 1, 1914, loose bowels May 7, with some insomnia, then she developed a typical erythema. Of her five children, three of the boys began at about the same time as their mother to show stomatitis and erythema. But apparently none show marked intestinal derangements. In A (Fig. 17) the mother showed, in March, 1911, typical erythema of hands and forearms followed by stomatitis, diarrhea and general weakness. The same year one of her eldest daughters had erythema of hands and arms lasting for four months. There was no recurrence in 1912, but in 1913 the hands were very red during May and June, but this was attributed to sunburn, despite the fact that she works in the mill all day. Her next younger sister, aged 18 years, had simply erythema of the hands and arms without other symptoms; these symptoms recurred in 1912, but were not present in 1913. The 8-year-old brother had also erythema of the hands and feet and the mouth was sore and there was diarrhea; he had some symptoms in 1912, but none in 1913. In this family the first, and sometimes the only effect, is an inflammation of the skin.

What, now, is the conclusion to be drawn from the facts that in the pellagra families some individuals are characterized only by severe skin symptoms, usually with inflammations of the lining of the mouth, others chiefly by severe intestinal symptoms, especially chronic diarrhea, and others by the predominance of mental symptoms. Why are these symptoms sometimes found associated two at a time or all three together? It seems most probable that we have to do in the different cases with biotypes that differ in the specific resistance or susceptibility of their different organs. That is, we have skin-susceptible biotypes, mouth-susceptible biotypes, intestine-susceptible biotypes, nerve-susceptible biotypes and other biotypes that are resistant in each of these respects or in two or more of them taken together.

An objection may be raised to referring in intestine-susceptible pellagra families to members who have had "typhoid fever." In justification I may say that many recent cases of pellagra have been diagnosed as typhoid fever, just as others have been as tuberculosis of the intestine or as eczema. The diagnoses of many physicians and coroners in our southern states have to be interpreted liberally. However, even an indubitable case of typhoid is significant; it implies that the individual tends to react to systemic poisoning by diarrhea, for such is the symptom upon which, combined with rash and high temperature, the diagnosis largely rests. The typhoid is then not significant as an equivalent of pellagra, but as an index of the individual's method of reacting to systemic poisoning, and, as such, it is justifiable to include such individuals in our pedigree of those nonresistant to intestinal symptoms.

IV. CONCLUSIONS

Pellagra is not an inheritable disease in the sense in which brown eye color is inheritable. The course of the disease does depend, however, on certain constitutional, inheritable traits of the affected individual.

Pellagra is probably communicable, but how the communicated "germ of the disease" shall progress in the body depends, in part, upon constitutional factors.

When both parents are susceptible to the disease, at least 40 per cent., probably not far from 50 per cent., of their children are susceptible; an enormous rate of incidence in a disease that affects less than 1 per cent. of the population on the average. While the high incidence is doubtless due to infection, it is also doubtless due to susceptibility, for right among the affected children grow up brothers and sisters who have never shown the symptoms of pellagra. We can understand this on the ground of inheritable differences in constitution of the children, just as brown eyes and blue eyes occur in the same family.

The importance of the constitutional factors is evinced by the difference in the reactions to the toxin of the disease shown by different families. Many families never show mental symptoms, while others usually do. In some families the intestinal symptoms are slight or negligible; in others severe and associated with early death. In some families the skin eruptions amount to little; other families are characterized by severe ulceration and desquamation of the derma. These family differences have all the characteristics of biotypes or blood lines, and afford the best proof that there is, indeed, a hereditary factor in pellagra.

Carnegie Institute of Washington, Department of Experimental Evolution.

In addition to the references cited in the text, the following may be consulted:

Babcock, J. W.: How Long Has Pellagra Existed in South Carolina, *Am. Jour. Insan.*, 1912, lxi, 185.

KEY TO CHARTS



Square indicates male.



Circle indicates female.



Solid black indicates skin symptoms.



Dots indicate mental symptoms.



Horizontal lines indicate intestinal symptoms



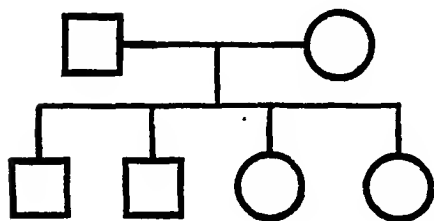
Indicates skin, nervous and intestinal symptoms, usually Pellagra.



d. inf. indicates died in infancy.



Number within square or circle indicates number of children of that sex.



Indicate husband and wife.

Indicate brothers and sisters.

Figure 1

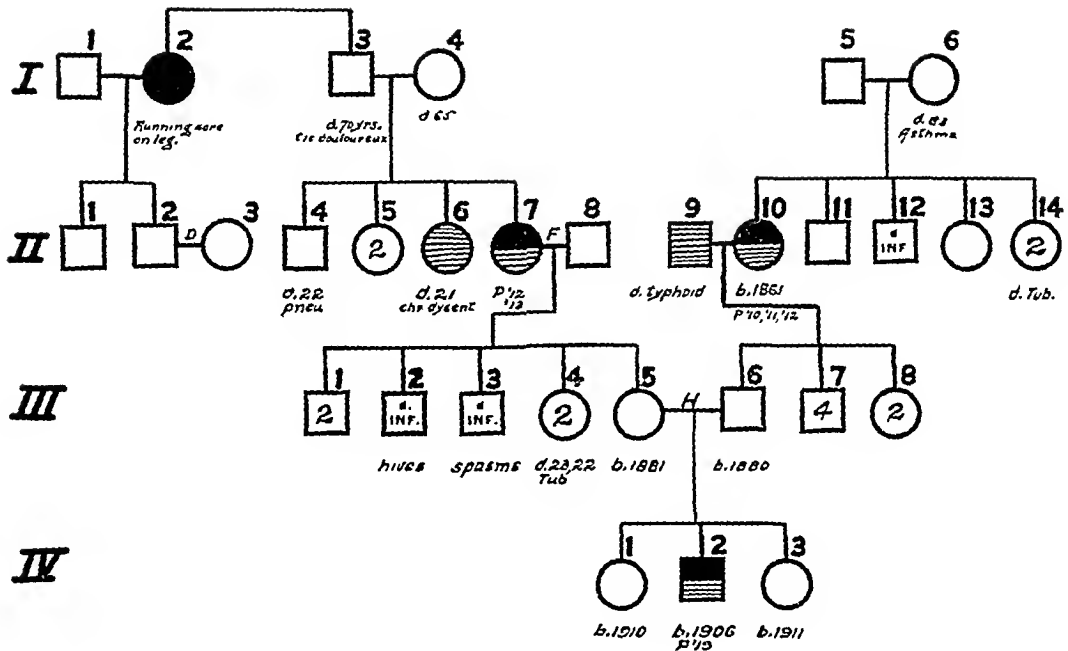


Figure 2

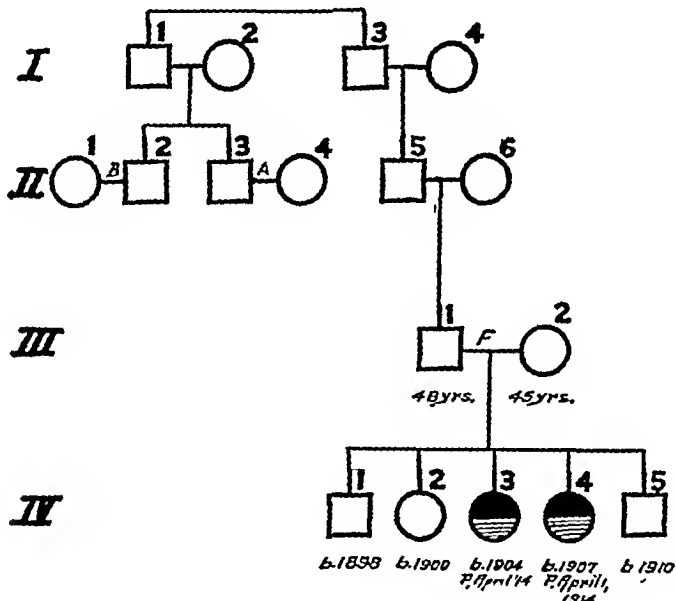


Figure 3

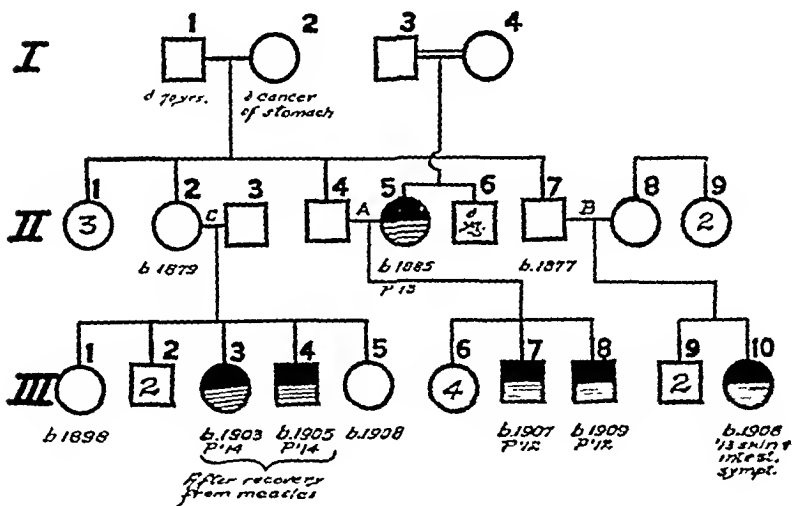


Figure 4

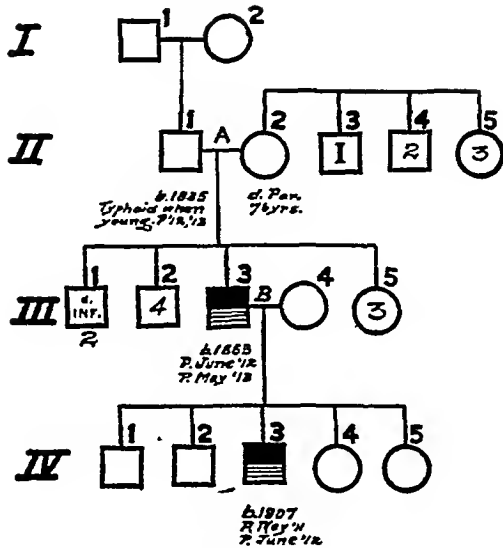


Figure 5

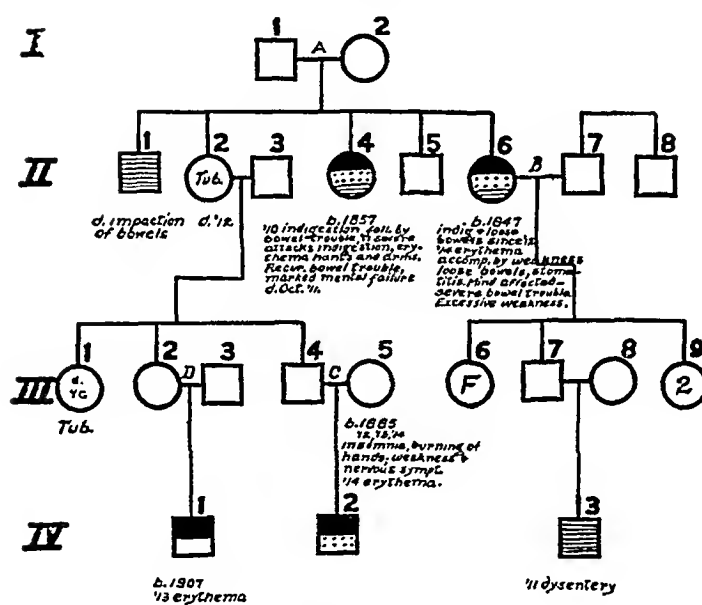


Figure 6

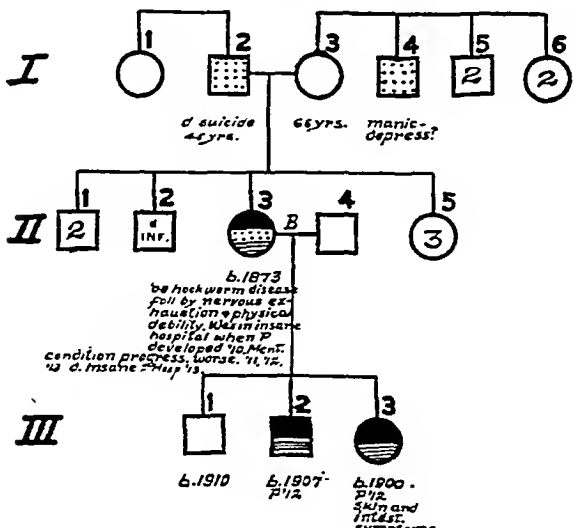


Figure 7

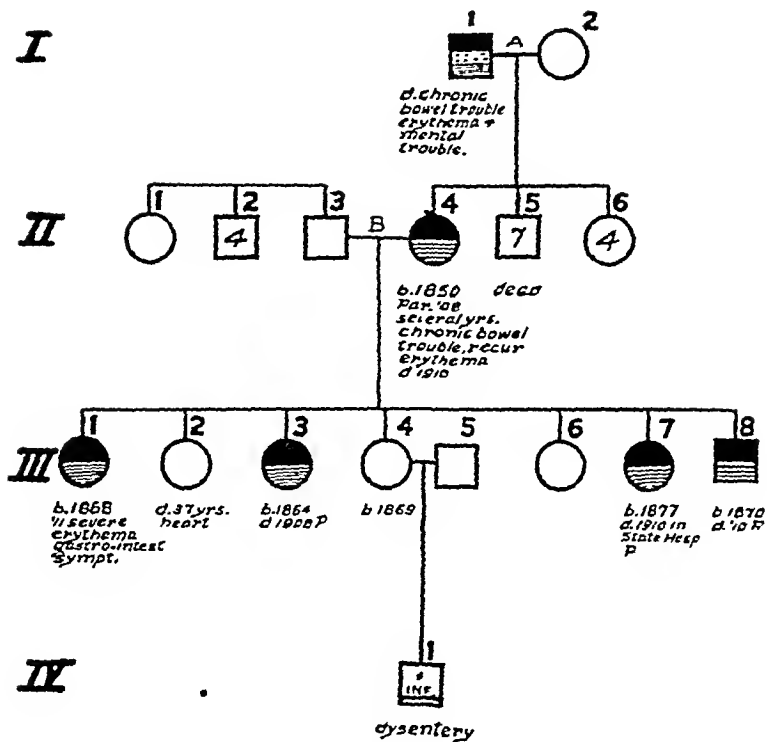


Figure 8

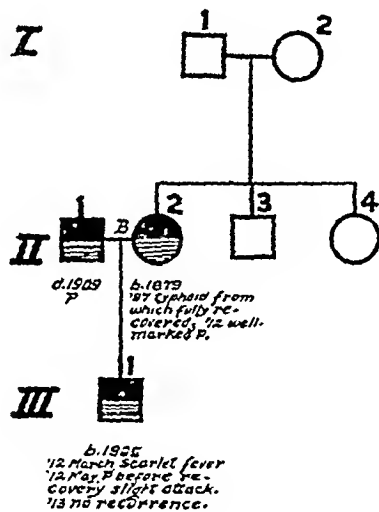


Figure 9

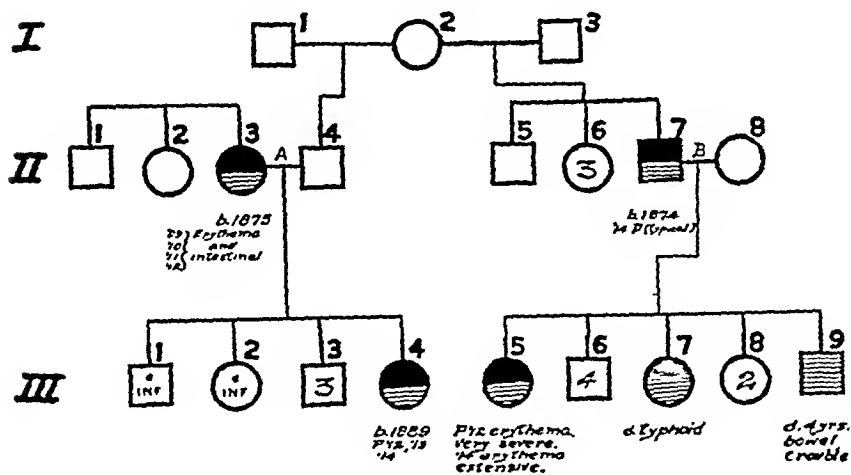


Figure 10

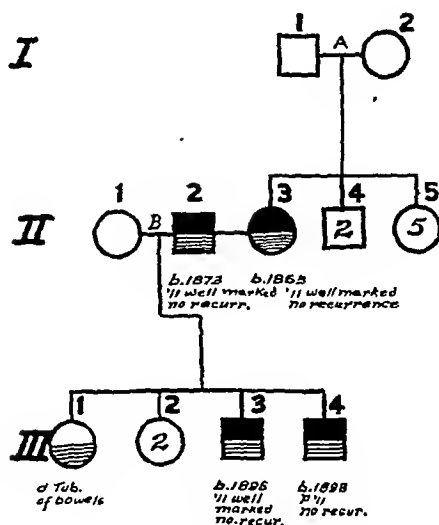


Figure 11

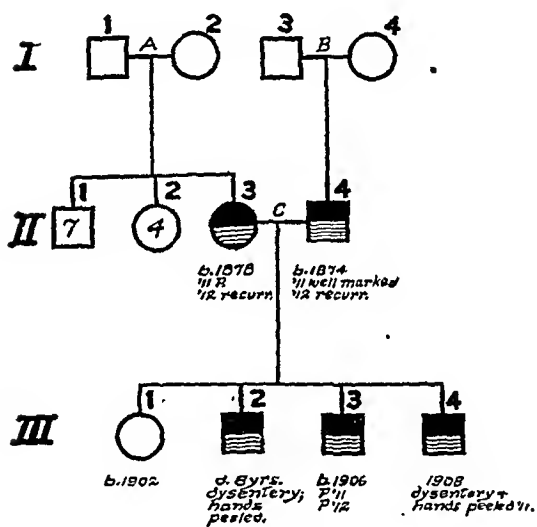


Figure 12

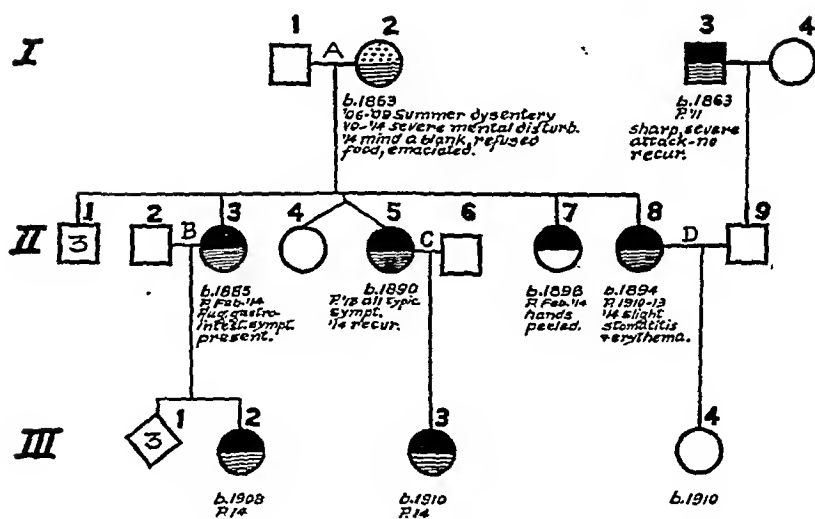


Figure 13

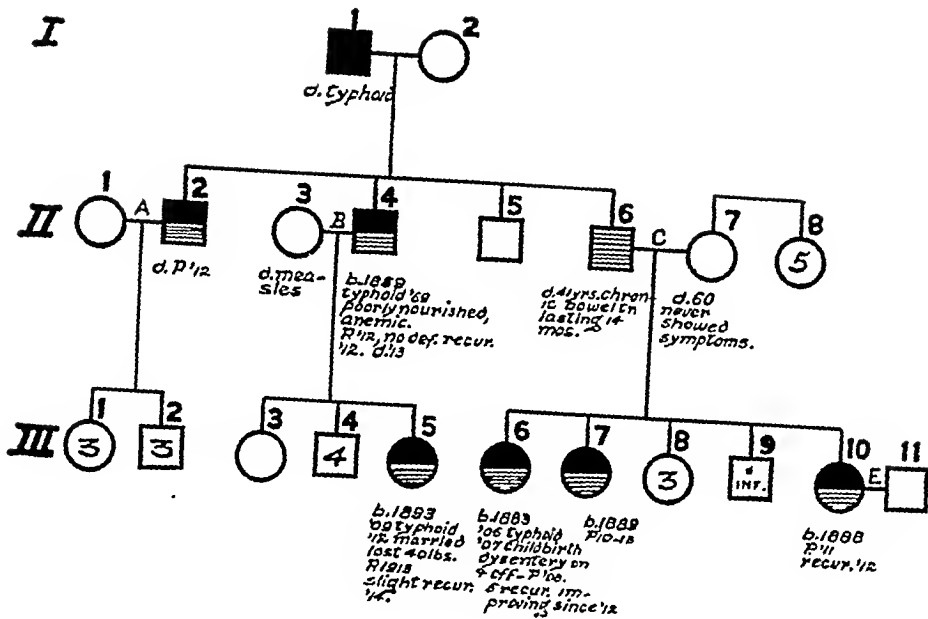


Figure 14

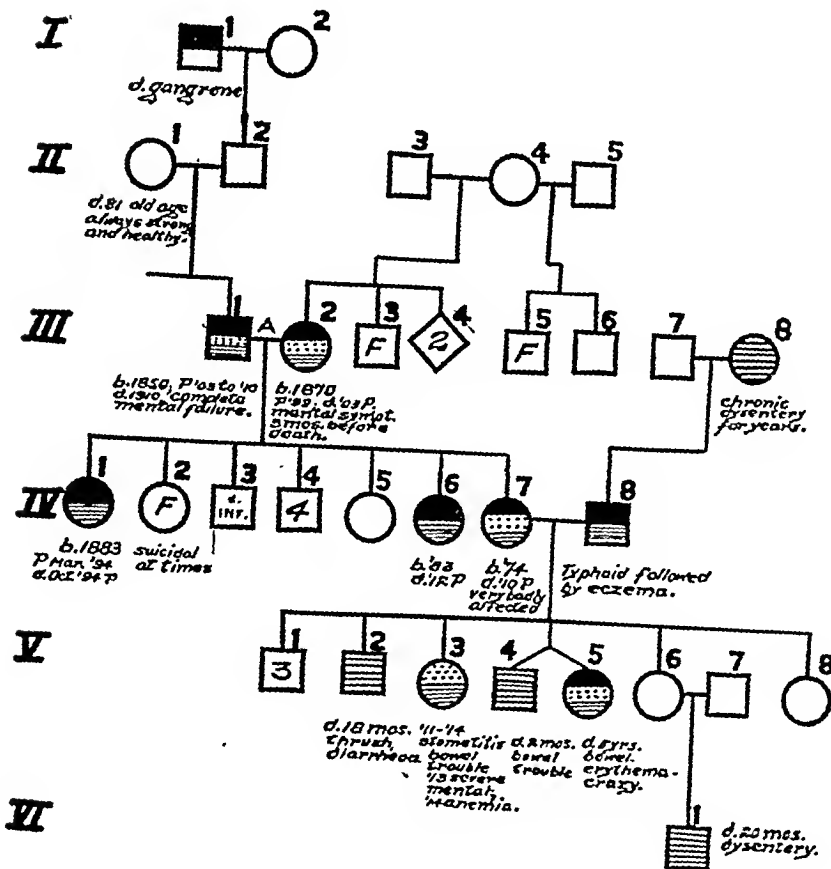


Figure 15

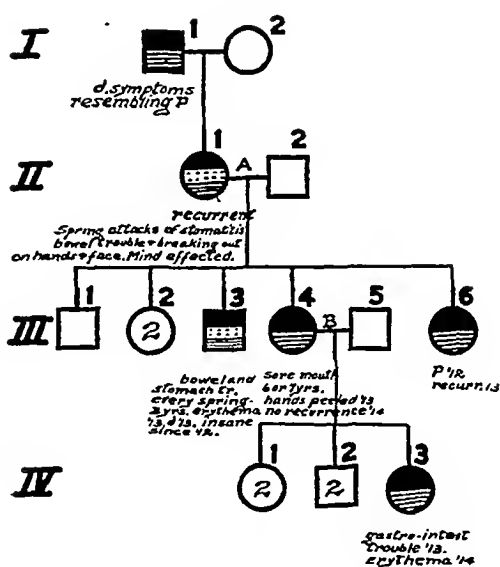


Figure 16

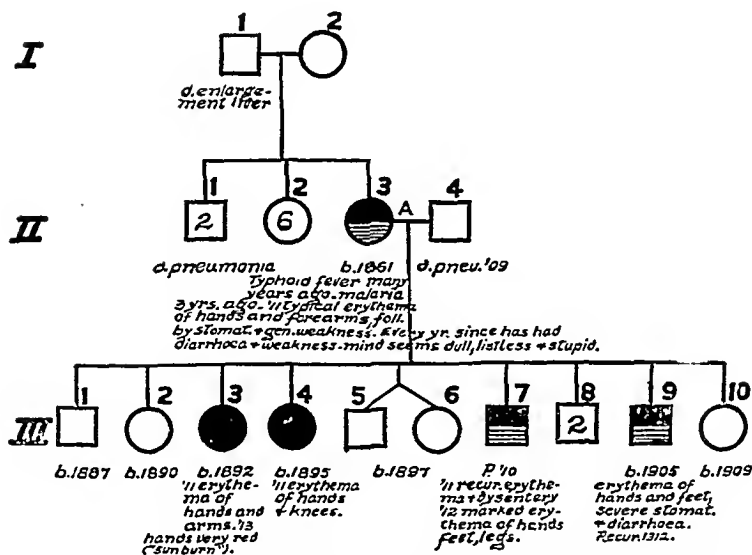


Figure 17.—In this cut III 9 should have been represented as of the female sex and should have been drawn a circle instead of a square.

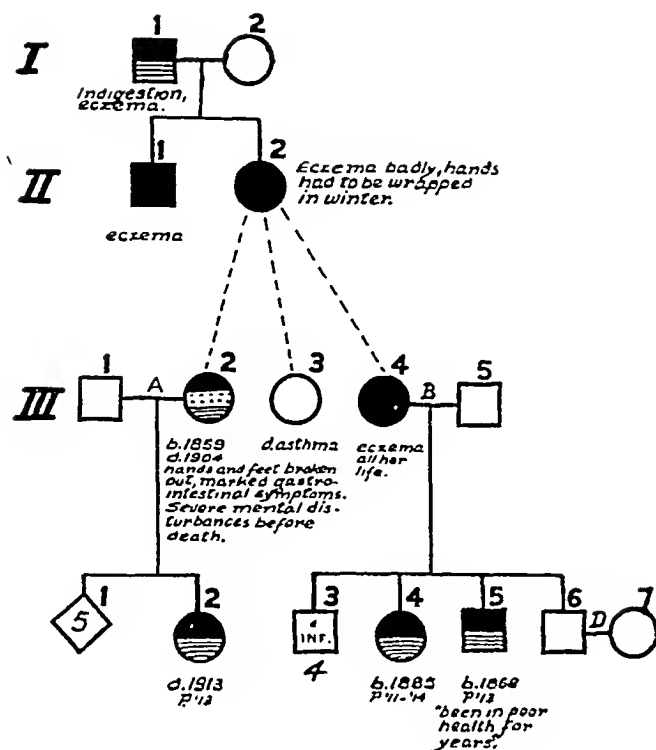


Figure 18

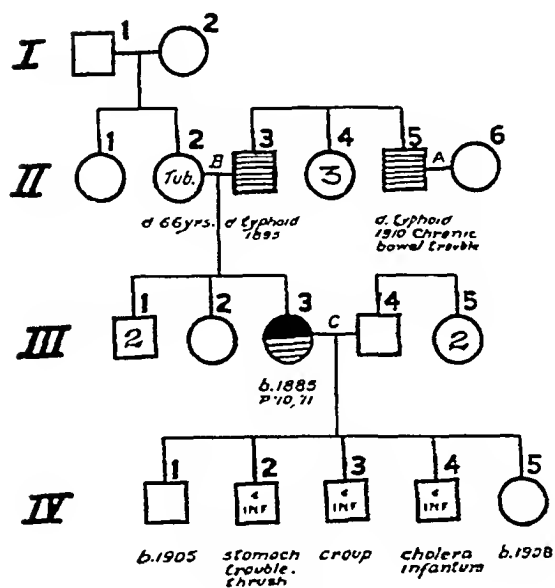


Figure 19

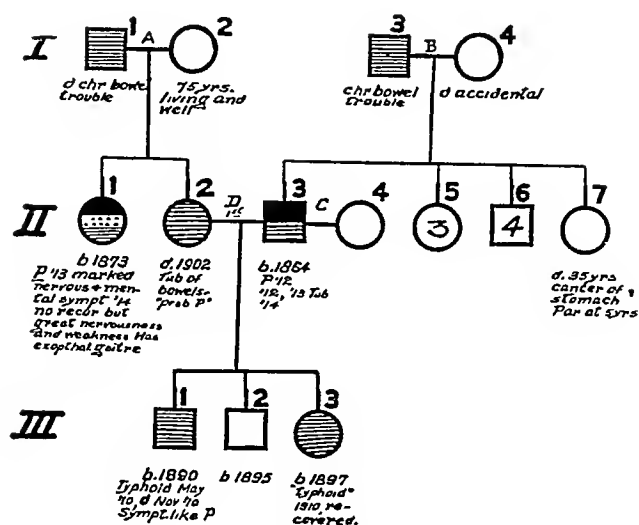


Figure 20

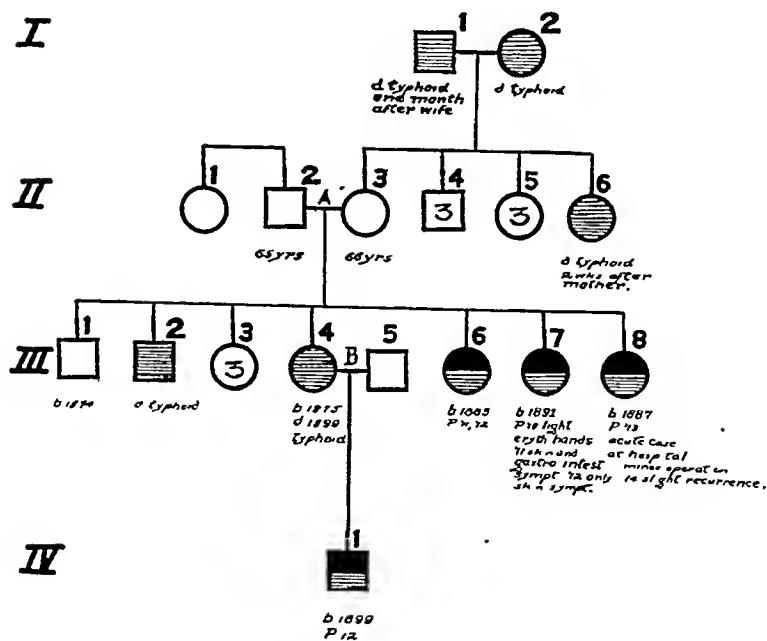


Figure 21

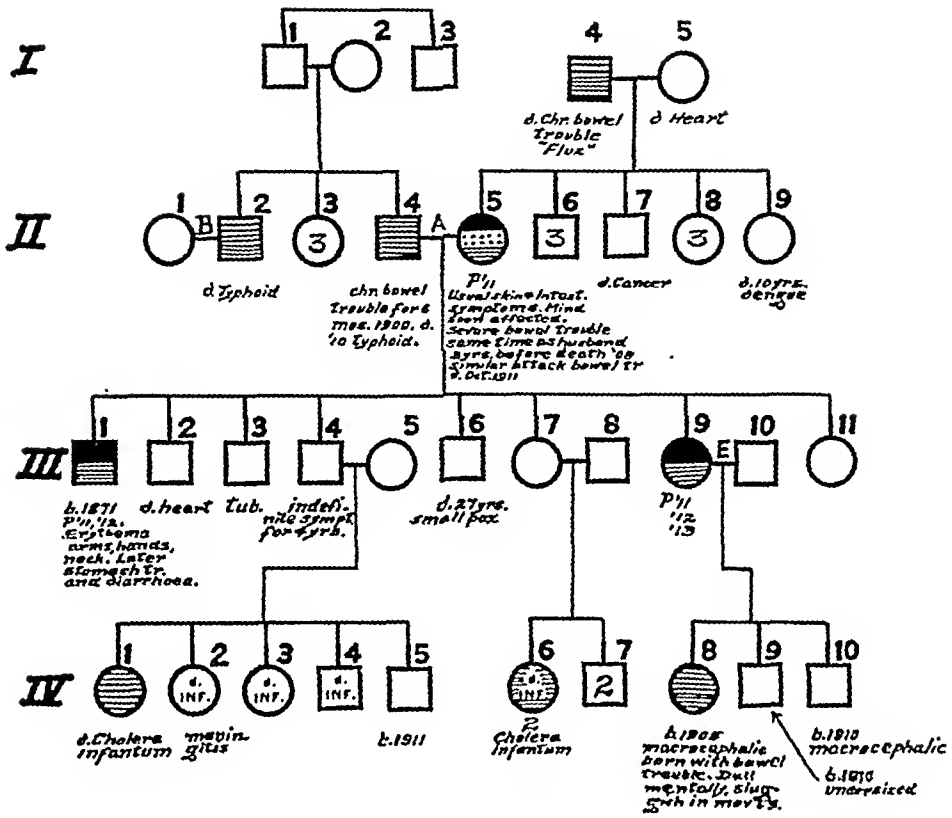


Figure 22

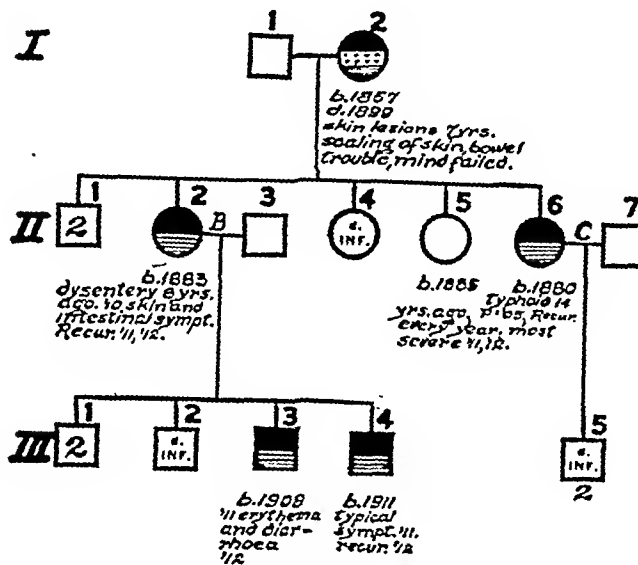


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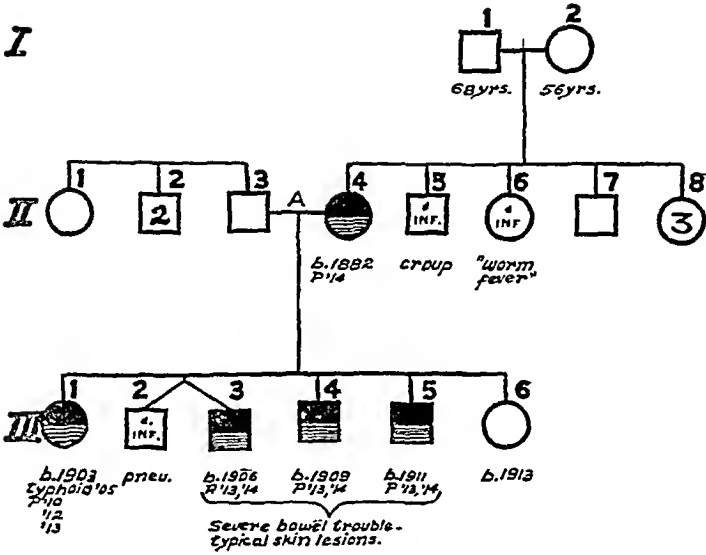


Figure 24

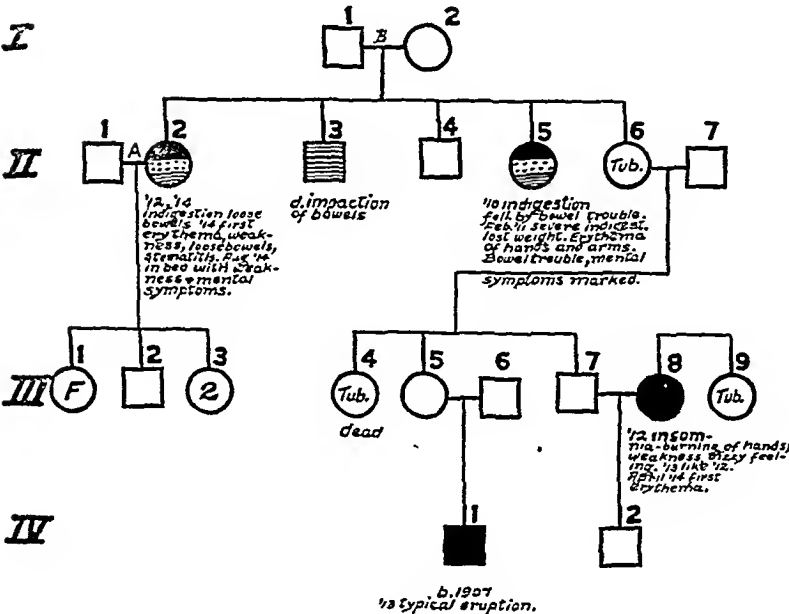


Figure 25

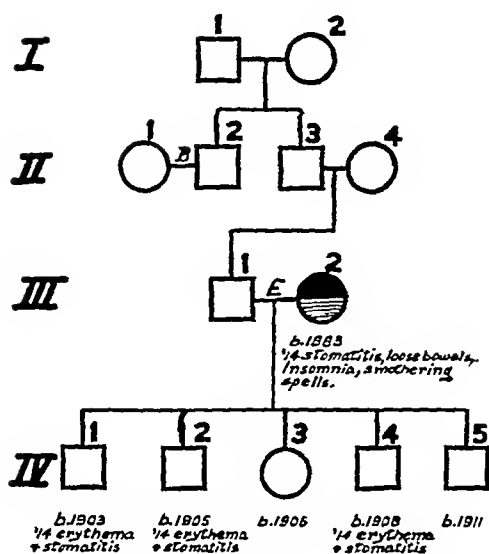


Figure 26

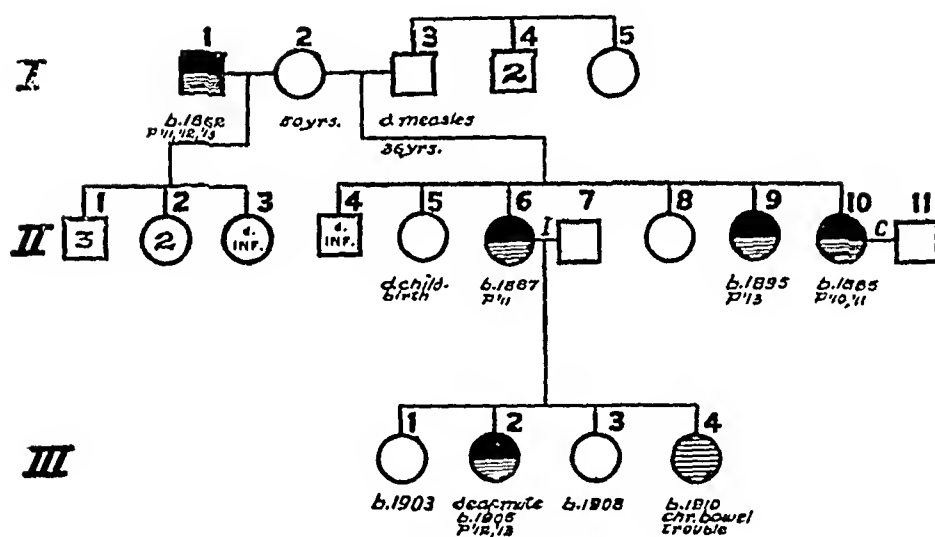


Figure 27

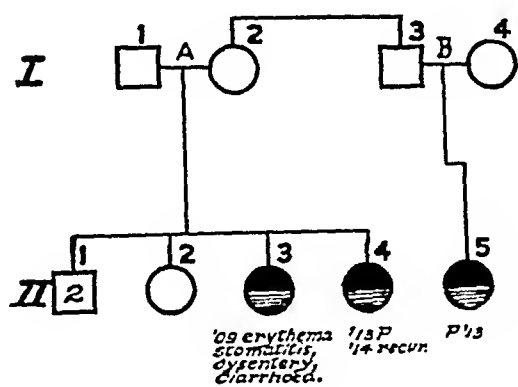


Figure 28

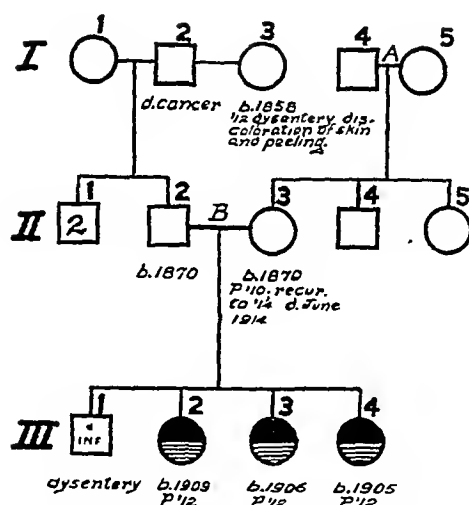


Figure 29.—In this cut the circle II 3 should have been drawn black in upper part and striped below, as in III 2, 3 and 4.

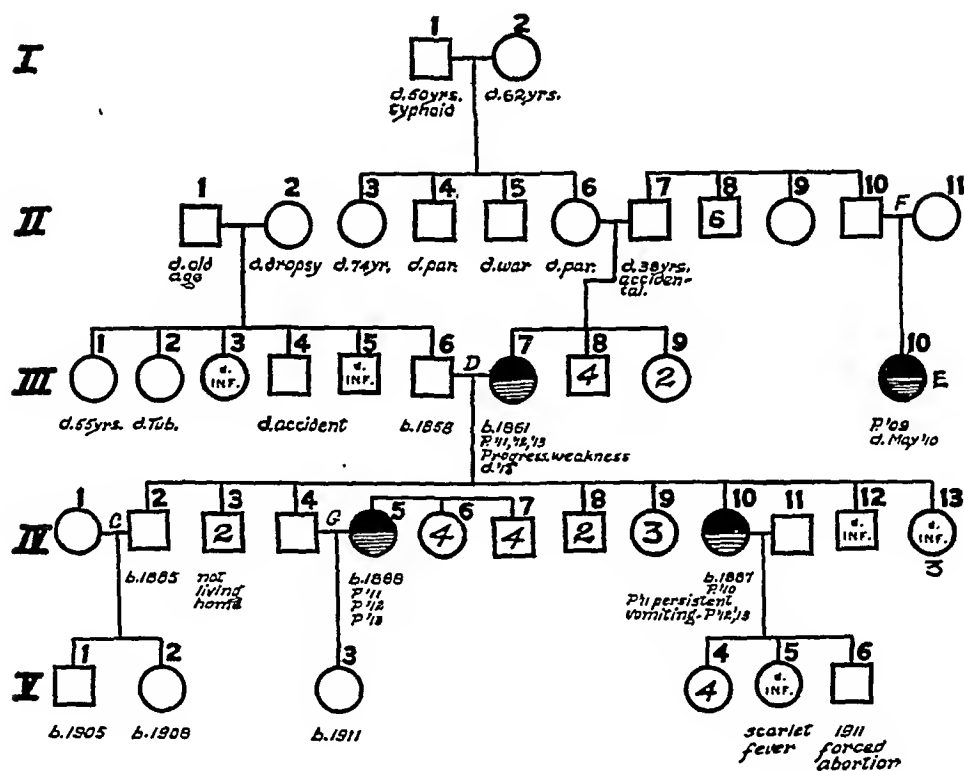


Figure 30

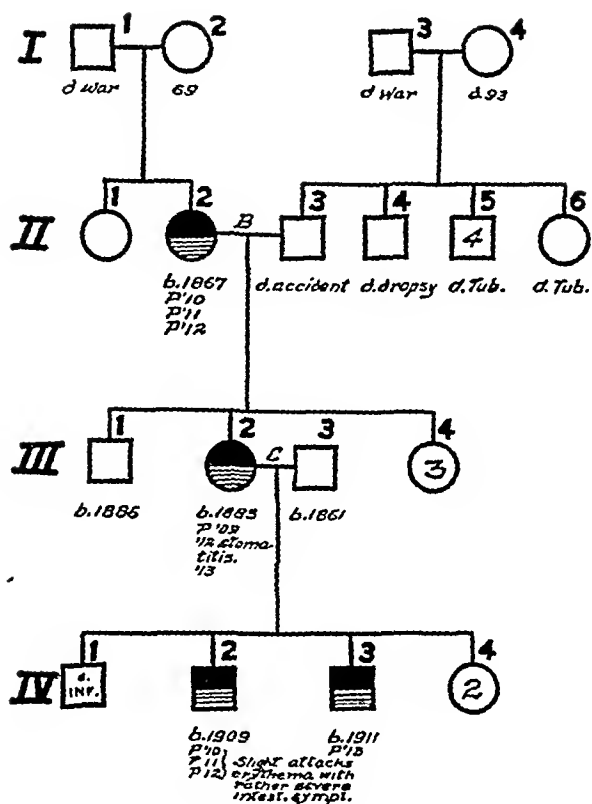


Figure 31

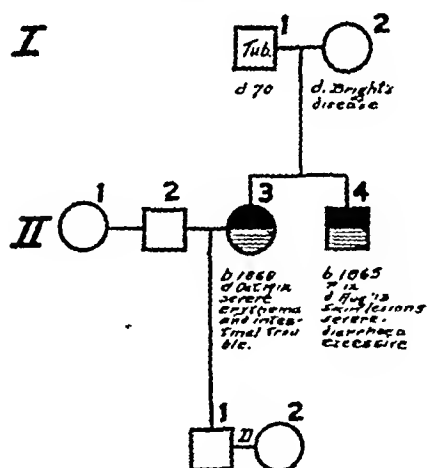


Figure 32

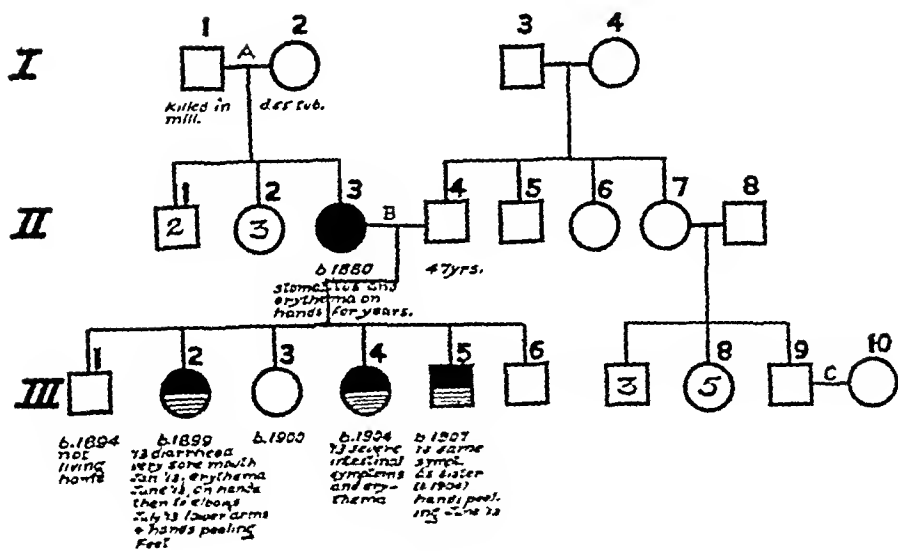


Figure 33

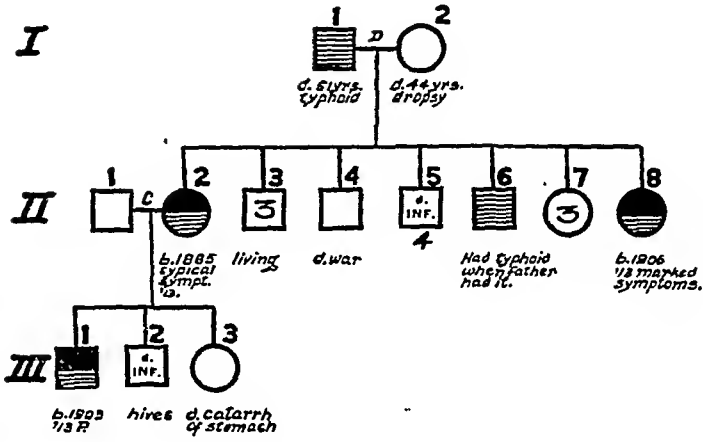


Figure 34

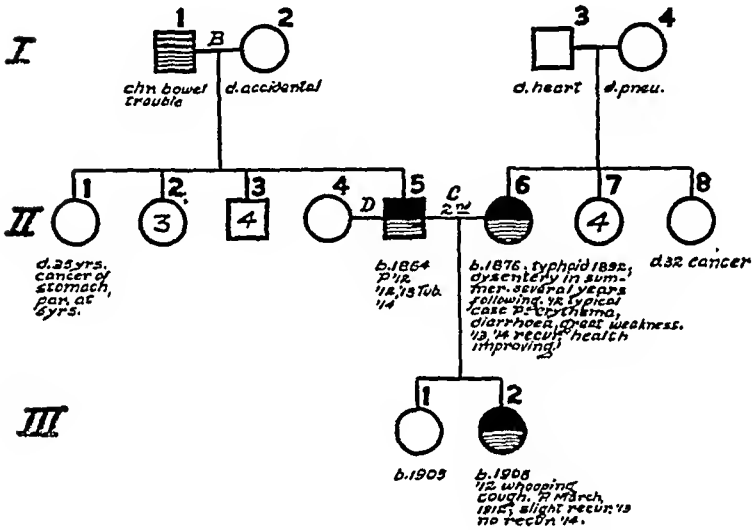


Figure 35

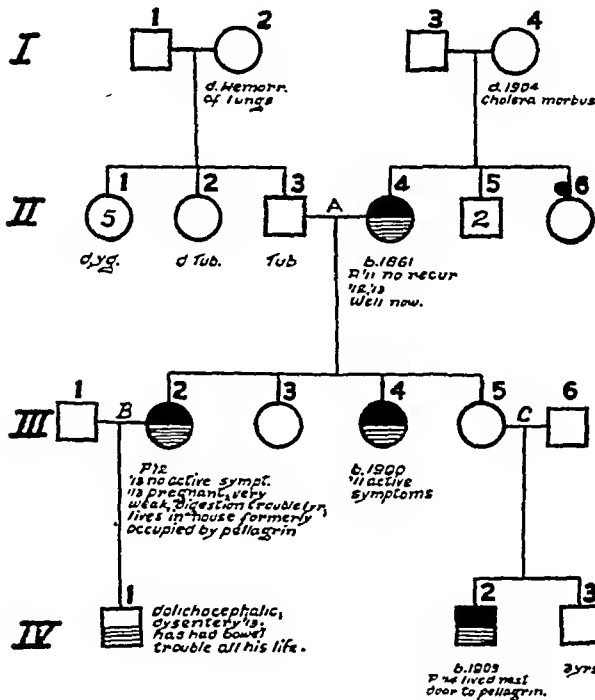


Figure 36

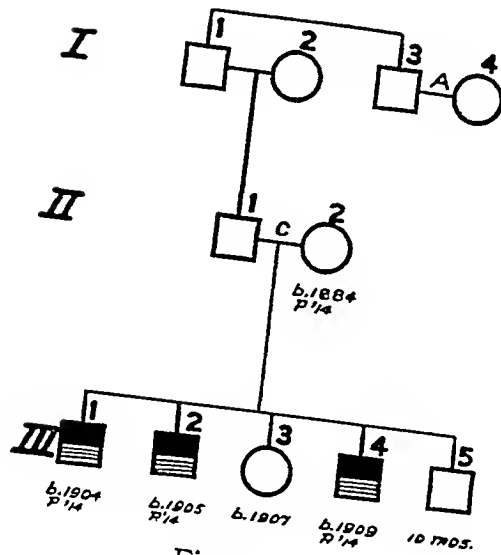


Figure 37

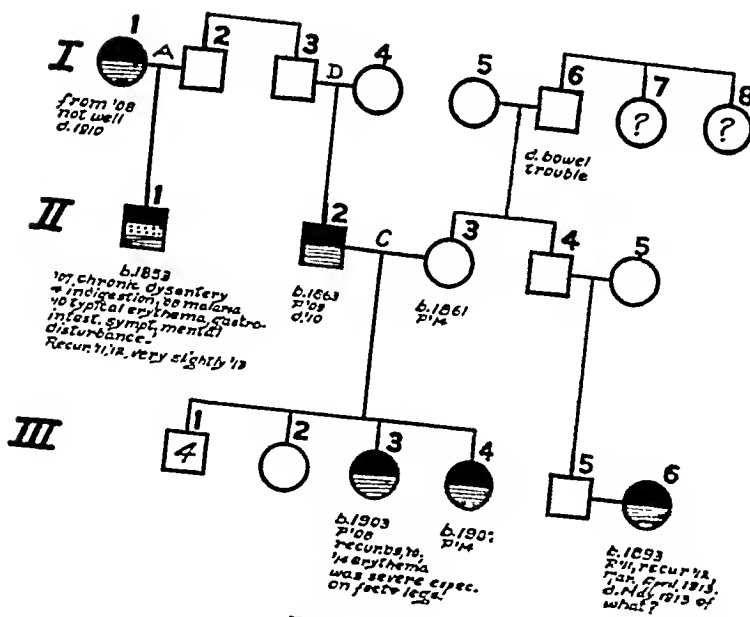


Figure 38

A STUDY OF THE HEREDITY OF PELLAGRA IN SPARTANBURG COUNTY, SOUTH CAROLINA *

ELIZABETH B. MUNCEY, M.D.

COLD SPRING HARBOR, LONG ISLAND, N. Y.

Early in the spring of 1913 the desirability of the study of pellagra from the viewpoint of heredity as a causative factor was brought to the attention of the Thompson-McFadden Pellagra Commission by Dr. Charles B. Davenport, Eugenics Record Office, Cold Spring Harbor, N. Y.

Under the joint patronage of the two offices fieldwork was begun in Spartanburg, June 1, 1913, and continued until Oct. 1, 1913. Through the winter the data collected were carefully reviewed, arranged in family groups and charted. It was found that in many instances more details were necessary, and the Thompson Pellagra Commission in 1914 decided that the results obtained were of sufficient merit to warrant another summer's work. Accordingly, fieldwork was begun May 1, 1914, and continued until Sept. 1, 1914. This year the association of pellagrins with antecedent cases was also carefully noted for comparison.

To study successfully the heredity of any disease it is necessary, first, for the disease to have been known through at least three generations; second, to have access to vital statistics; third, to review family records; and fourth, to interview various members of a family so that statements may be corroborative. The mill villages in South Carolina are not fertile fields for such study, because, first, pellagra has been generally recognized in the South only about twenty-five years, less than one generation; second, in many sections no vital statistics are recorded, or if so, they are so incomplete as to be of little value; third, the majority of families keep no family record; and fourth, while the persons interviewed were in most cases willing to give all the information they could, in many instances they were entirely ignorant of their family histories outside of their own households.

Recognizing the difficulty of presenting a study so imperfect in detail, yet, with a view to establishing a foundation for future study,

* Submitted for publication March 9, 1916.

* From the Eugenics Record Office of the American Genetic Association and the Department of the Laboratories, New York Post-Graduate Medical School and Hospital. This paper forms a part of the Third Report of the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

we have gathered all possible data, have discarded anything we considered in any way inaccurate, and present herewith the results of the eight months' work.

Every family reported was visited, and as far as possible the members of the households were seen. All possible family history was collected and tabulated. The causes of death, the prevalence of disease, congenital weakness and diseases of the intestinal tract, skin diseases and mental diseases were carefully noted.

Eczema was reported fourteen times, insanity thirteen times, feeble-mindedness twelve times, morphin addiction three times, deaf-mutism ten times, brachydactylism three times, hydrocephalic children twice, dolichocephalic child once, harelip once.

This does not show a larger proportion of any disease than one might expect from the study of an equal number of individuals taken from any nonpellagrous community of similar status.

The history of forty-five colored pellagrins in thirty-five households was taken. Of these, there were twenty-eight female and seventeen male. They knew so little of their family history—many not even knowing their fathers' names—that the study of inheritance was not undertaken.

The family histories of 555 white pellagrins were studied, which involved a partial history of 1,872 households, 786 of which were visited.

The families were grouped according to the number of pellagrins into six groups (see Table 1) as follows:

- Group I, one pellagrin in family.
- Group II, two pellagrins in family.
- Group III, three pellagrins in family.
- Group IV, four pellagrins in family.
- Group V, five pellagrins in family.
- Group VI, more than five pellagrins in family.

In Group I, one pellagrin in a family, there were seventy-three parents with 248 children—201 living and forty-seven dead, 172 living at home with the parents. None of these had recognized pellagra, although fourteen children died with intestinal trouble after the mother developed pellagra. One died with measles and dysentery, aged 11 months; seven with bowel trouble, ages ranging from 3 to 21 months; one with thrush and pneumonia, aged 11½ years; one with hives, aged 3 months; one with hives and stomach trouble; one with dysentery and rash, aged 2 years; one with rash, sore mouth and diarrhea, aged 14 months.

Dr. Simonini recognizes two kinds of pellagra in childhood: (1) pellagra with cutaneous symptoms; (2) pellagra without cutaneous

symptoms. In all probability the fourteen cases cited above would have been classed by him as pellagra without cutaneous symptoms.

In one of these families, the grandfather, 75 years of age, has had indigestion for years. The great-grandfather died of tuberculosis of the bowels. Several members of the grandmother's family died of

TABLE 1.—DISTRIBUTION OF PELLAGRINS AND THE NUMBER OF FAMILIES, HOUSEHOLDS AND INDIVIDUALS IN EACH GROUP

Group	Pellagrins			Families	Households	Individuals
	Female	Male	Total			
I.....	83	22	105	105	626	2,259
II.....	72	30	102	51	306	1,056
III.....	71	31	102	34	380	1,027
IV.....	51	29	80	20	80	637
V.....	78	32	110	22	309	1,073
VI.....	39	17	56	7	171	644
Total.....	394	161	555	239	1,872	6,696

TABLE 2.—THE RELATIVE PROPORTION IN WHICH THE DIFFERENT MEMBERS OF A FAMILY WERE AFFECTED WITH PELLAGRA

Group	Mothers	Fathers	Wives*	Daughters	Sons	Total
I.....	63	10	7	12	13	105
II.....	45	14	..	27	16	102
III.....	40	17	10	21	14	102
IV.....	27	11	4	20	18	80
V.....	49	12	9	20	20	110
VI.....	21	10	2	18	5	56
Total.....	245	74	32	118	86	555
Rate per cent.	44	13.4	5.8	21.3	15.5	100

* Married women who have not borne children.

typhoid. The mother, Case 18, had typhoid in 1907 and developed pellagra in 1910. One child, born in 1911, died at the age of 3 months of bowel trouble; four other children are living and well.

In one family the grandmother died with chronic bowel trouble. Maternal uncles died with dysentery. Mother, Case 612, developed

pellagra in 1910. One daughter died in infancy with hives. One son died in infancy with bowel trouble. Seven other children are living and well.

In one family the grandmother died insane. In the mother's fraternity there were four infant deaths, and three births before term. The mother, Case 37, developed pellagra in 1908 and has had yearly recurrences ever since, always accompanied with severe mental symptoms. One son died at 2 years of age with dysentery and rash, one daughter died at 1½ years of age, with thrush and pneumonia. Two girls, aged 12 and 8, are living and unaffected.

In Group I, it is possible to trace an inherited weakness from the grandparents in twelve cases:

Case 18, one great grandfather died with tuberculosis of bowels.

Case 606, one grandfather died of typhoid.

Case 687, one grandfather died insane.

Case 612, one grandmother died with chronic bowel trouble.

Case 54, one grandmother died with dysentery.

Case 541, one grandmother died with dysentery.

Cases 693, 521 and 281, three grandmothers died of typhoid.

Case 37, one grandmother died insane.

Case 611, one grandmother died with indigestion.

In Group II, two pellagrins to a family, the fifty-nine parents had thirty pellagrous children and 153 nonpellagrous. There were thirteen pellagrous children with nonpellagrous parents, and forty-three brothers and sisters not pellagrous. Four children died after their mother developed pellagra. One died with hives at 4 months; one with dysentery at 5 months; and twins miscarried.

Inherited weakness was traced from the grandparents in eight cases:

Case 713, one great grandmother died with colic and the grandfather had pellagra in 1911, 1912 and 1913.

Case 81, one great-grandmother died with stomach trouble, and the grandmother developed pellagra in 1911.

Cases 107, 130 and 703, three grandmothers were pellagrins.

Case 160, one grandmother died insane.

Case 944, one grandfather died of pellagra in 1912.

Case 601, one grandfather died with typhoid.

In Group III, three pellagrins to a family, the fifty-seven parents had twenty-four* pellagrous children and 119 nonpellagrous. Twenty-one children were pellagrous in the same household with unaffected parents and sixty unaffected brothers and sisters. Four children died after their mother developed pellagra, one dying with marasmus, one with bowel trouble, one with hives, one with dysentery and hands peeling.

* Those pellagrins designated as wives in Table 2 are included here in the group of children.

In one family the grandfather committed suicide. Insanity ran in the grandmother's family. The mother, Case 25, developed pellagra in 1910 with marked mental symptoms. She died in 1913 in an asylum. Two children, one boy and one girl, developed pellagra in 1912. The youngest child, 4 years of age, is unaffected.

Inherited weakness is traced to grandparents in five cases:

Case 25, one grandfather committed suicide, and several members of the grandmother's family were insane.

Case 162, one grandfather died with typhoid; the father and son were both pellagrins.

Case 366, one grandfather died with bowel trouble; the mother and daughter were both pellagrins.

Case 526, one paternal grandfather died of bowel trouble; the father, daughter and mother were pellagrins.

Case 432, one grandfather died in 1901 of pellagra and insanity; mother and daughter are both pellagrins.

In Group IV, four pellagrins to a family, thirty-eight pellagrous parents had twenty-five pellagrous children and eighty-one nonpellagrous, while seventeen children were pellagrous in the same household with unaffected parents and thirty-eight unaffected brothers and sisters.

Inherited weakness was traced to grandparents four times:

Case 55, one great-grandmother died in 1904 with bowel trouble; the grandmother developed pellagra in 1911, the mother in 1912, and the son, aged 2 years, was dolichocephalic. His bowels were bad from birth. One great-grandson from another line of descent developed pellagra in 1913.

Case 83, one grandmother developed pellagra in 1910; the mother developed pellagra in 1909 and two sons developed the disease in 1913. One son died in infancy, cause unknown.

Case 132, one grandfather died in 1909 with pellagra and insanity. The grandmother developed pellagra in 1910. They had fifteen children, six of whom died in infancy. None of the children developed pellagra, but two grandchildren developed it in 1913.

Case 565, one maternal grandfather died of pellagra in 1909. The mother and son developed it in 1911 and the father, whose family history is negative, developed it in 1912.

In Group V, five pellagrins to a family, the sixty-one pellagrous parents had thirty-eight pellagrous children and 140 nonpellagrous. Eleven children were pellagrous in the same household with unaffected parents, and thirty-four unaffected brothers and sisters. Inherited weakness was traced to grandparents in three cases.

Case 308, one grandmother died of pellagra in 1900. The mother developed pellagra in 1910, her two sons in 1911, and the mother's sister in 1905. This sister had twins, who died three weeks after birth, and no other children.

Case 392, one grandfather died of chronic bowel trouble. The mother died of pellagra in 1910. Two daughters died of pellagra in 1908 and 1910. One son died of pellagra in 1910. One daughter, living, developed pellagra in 1911 and has recurrence yearly. She had eight children, two of whom died in infancy. (Fig. 19, R Family for other case.)

In Group VI, more than five pellagrins to a family, the thirty-one parents had twenty pellagrous children, and sixty-five nonpellagrous. Five children were pellagrous in the same household with unaffected parents and twenty-one unaffected brothers and sisters.

TABLE 3.—COMPARATIVE INCIDENCE OF PELLAGRA AMONG CHILDREN WITH NONPELLAGROUS PARENTS, WITH ONE PELLAGROUS PARENT AND WITH TWO PELLAGROUS PARENTS

Group	Parents		Children	
	Pellagrous	Nonpellagrous	Pellagrous	Nonpellagrous
With nonpellagrous parents:				
I.....	0	58	32	84
II.....	0	41	23	43
III.....	0	81	45	60
IV.....	0	30	17	38
V.....	0	19	11	34
VI.....	0	10	5	21
Total.....	0	239	133	280
With one pellagrous parent:				
I.....	73	...	0	172
II.....	55	...	30	134
III.....	47	...	20	106
IV.....	26	...	17	54
V.....	55	...	38	124
VI.....	21	...	15	42
Total.....	277	...	120	632
With both parents pellagrous:				
I.....	4	...	0	10
II.....	10	..	4	13
III.....	12	...	8	27
IV.....	6	...	0	16
V.....	10	...	10	23
VI.....	0	...	0	0
Total.....	42	...	22	98
Grand total.....	319	...	275	1,010

In Table 3 there are twenty-one matings of forty-two parents with both parents pellagrous. They have 120 children, twenty-two pellagrous and ninety-eight nonpellagrous. There are 277 matings of 554 parents with only one parent showing pellagra. They have 752 children, 120 pellagrous and 632 nonpellagrous. If pellagra were an heredi-

TABLE 4.—RELATIONSHIP EXISTING WHEN THERE WERE TWO OR MORE PELLAGRINS IN A FAMILY

Relationship*	Groups						
	I	II	III	IV	V	VI	All Groups
M and D only.....	..	13	7	3	6	5	34
M and S only.....	..	4	3	1	1	1	10
M, D, and S.....	4	4	4	1	13
M and any child.....	..	17	14	8	11	7	57
F and D only.....	..	6	2	1	3	1	13
F and S only.....	..	2	..	1	3
F, D, and S.....	1	1
F and any child.....	..	8	3	2	3	1	17
M, F and D.....	2	2
M, F and S.....	3	2	5
M, F, D and S.....	1	1
M, F and children.....	3	2	..	3	8
Total number of individuals of each class:							
Mother.....	63	45	40	27	49	21	245
Father.....	10	14	17	11	12	10	74
Daughter.....	12	27	21	20	20	18	118
Son.....	13	16	14	18	20	5	86
Total.....	98	102	92	76	101	54	523

* In this table M signifies mother; F, father; D, daughter, and S, son.

tary trait we might expect in the first instance ninety pellagrous children instead of twenty-two, and in the second instance at least 158 instead of 120. The 133 pellagrous children from unaffected parents would also demand explanation. Where did their susceptibility to the

disease originate? Again, the fact that in almost every instance the second or the third member of a family developed pellagra within a few weeks or months of the time of the incident case strengthens the indication that the disease is not transmitted by heredity.

In Table 4 there are 245 mothers in all groups, sixty-five, or 26.3 per cent., with pellagrous children, and 180, or 73.5 per cent., without pellagrous children, nearly three times as many without as with pellagrous children.

TABLE 5.—RELATIONSHIP OF PELLAGRINS IN FAMILIES WITH PELLAGRA IN THE THIRD GENERATION

1 grandmother (1911-1913)	1 granddaughter (1914)	Direct
2 grandmothers (1893-1911) (1910-1913)	1 grandson (1913)	Direct
1 grandfather (1912)	Mother (1913-1914)	2 granddaughters (1913-1914)	Direct
1 grandfather (1909)	[Grandmother] (1911)	2 granddaughters (1913)	Direct
1 grandfather (1912-1913)	Father (1912-1913)	1 grandson (1911-1912)	Direct
1 grandfather (1901)	Mother (1907-1913)	1 granddaughter (1911-1913)	Direct
1 grandmother (1910-1912)	Mother (1909-1913)	2 grandsons (1910-1913)	Direct
1 grandfather (1908)	Mother (1904-1913)	2 grandsons (1912)	Direct
1 grandmother (1910-1912)	Mother (1909-1913)	2 grandsons (1910-1912) (1913)	Direct
1 grandmother (1900)	2 mothers (1905) (1910-1911)	2 grandsons (1911-1912)	Direct
1 grandmother (1910-1914)	4 daughters (1910) (1913) (1914)	2 granddaughters (1914)	Direct
1 grandfather (1913)	Son-in-law (1912-1913)	1 granddaughter (1914)	Direct and indirect
1 grandfather (1910-1912)	Daughter-in-law (1912-1913)	2 grandsons (1913) (1914)	Direct and indirect
1 grandfather (1909)	Daughter and son-in-law (1911-1913) (1912)	1 grandson (1911)	Direct and indirect
1 grandmother (1910)	Son and daughter-in-law (1910-1912) (1910)	3 grandchildren (1912)	Direct and indirect
There are also 1 step-grandfather (1911-1914)	3 stepchildren (1910) (1910) (1913)	2 step-grandchildren (1910) (1913)	
1 step-grandmother (1912)	1 stepdaughter (1910-1914)	3 step-grandchildren (1912)	

There are seventy-four fathers in all groups, twenty-five, or 33.8 per cent., with pellagrous children, and forty-nine, or 66.2 per cent., without pellagrous children, nearly twice as many without as with pellagrous children. The frequency with which mother and daughter only are affected is nearly three and one-half times the frequency with

which the mother and son only are affected. The frequency with which father and daughter only are affected is four times that when father and son only are affected. There is no definite explanation of this excessive number of daughters affected, it may be partially explained by the greater prevalence of pellagra in girls between the ages of 15 and 20. This is not borne out, however, by the number of pellagrins of the two sexes in our study where we have 118 daughters and eighty-six sons. The question arises whether the closer contact of the daughter with parents in the mill villages studied may not be a large factor in this excess. The boys from the time they can walk until the time when they go to work in the mill spend most of the time, except when sleeping, on the streets.

TABLE 6.—CAUSES OF DEATH IN ADULTS

Groups	I	II	III	IV	V	VI	Total
Typhoid.....	..	32	17	9	8	26	92
Chronic bowel trouble or dysentery.....	3	10	9	7	5	14	48
Indigestion.....	..	5	6	3	5	19	38
Tuberculosis.....	..	12	2	10	12	17	53
Heart.....	..	8	1	4	2	10	25
Paralysis, without specified cause.....	..	15	2	6	3	5	31
Kidney trouble.....	..	8	4	3	2	3	20
Pneumonia.....	..	4	4	3	3	3	17
Dropsy, without specified cause.....	..	6	2	1	1	6	16
Cancer.....	..	4	1	2	2	3	12
Suicide.....	1	1	..	5	7
Asthma.....	..	4	..	2	..	1	7
Rheumatism.....	..	4	2	1	7
Epilepsy.....	..	1	4	7	12

There are fifteen families in which grandparents are affected. These have been counted as members of one family, although the descent is not always in a direct line. The relationships are shown in Table 5.

If there were a sufficient number of cases, this table would appear to indicate heredity, but when we consider the 596 parents in our study and find that they should have had over 2,000 grandfathers, the number of affected grandparents, namely, fifteen, is an insignificant quantity.

In every instance except the last two cases, the disease has occurred coincidentally or within a year or two in the grandparents and the other members of the family. In every instance except the two last men-

tioned, there has been direct family contact. Lombroso says: "Often the influence of heredity is not demonstrable because the grandparental influence escapes the slight interest of the poor country people, although atavistic heredity is more common than from father and mother." Strambio wrote that the greater part of pellagrins are born of pellagrous parents, and that the offspring of these has a decided disposition for taking the disease. A study of these same families during twenty or thirty years would be necessary to confirm this statement.

Accurate death reports were impossible to obtain, but wherever the causes of death were actually known they were recorded.

TABLE 7.—CAUSES OF INFANT DEATH

Diseases	Groups						Total
	I	II	III	IV	V	VI	
Bowel trouble or dysentery.....	8	2	4	4	15	5	38
Whooping-cough.....	3	2	6	1	12
Hives.....	3	1	3	..	2	2	11
Pneumonia.....	2	2	1	..	4	2	11
Catarrh of stomach.....	3	2	1	..	2	..	8
Cholera infantum.....	1	1	2	1	..	2	7
Thrush.....	3	2	1	6
Marasmus.....	1	2	1	1	5
Meningitis.....	2	1	..	1	4
Measles.....	..	1	1	1	3
Peritonitis.....	1	1	2
Born dead.....	10	3	13
Unknown.....	62	35	26	12	23	24	182
Total known.....	27	13	13	6	41	20	120

No record was made of deaths from diphtheria, scarlet fever, malaria, measles, erysipelas or smallpox.

Table 6 is of value only in showing the relatively high proportion of typhoid fever and stomach and bowel trouble in the families in which there were more than one pellagrin.

Under the date of Oct. 23, 1909, Acting-Assistant Surgeon Sams¹ of the U. S. P. H. S. reported from Charleston as follows: "Pellagra, as such, has but recently been recognized in this city, the first case

1. Sams: Pub. Health Rep., 1909, xxiv, 1657.

having come under treatment in March, 1908. There is a very general impression among the local physicians that pellagra has existed in the city for probably twenty years or more, and been incorrectly diagnosed as eczema, dysentery, intestinal tuberculosis, etc., with dementia as a complication, or the reverse."

J. W. Babcock,² M.D., superintendent of State Hospital for Insane, Columbia, S. C., adds several others: "syphilis, malaria, acute delirium, hookworm, dermatitis exfoliativa, tuberculosis of the skin, liver spots, scurvy, neurasthenia, meningitis, nurse's sore mouth, sprue, meningo-encephalitis, neuritis, etc."

This table simply shows a record of the infant deaths in the households visited. It was impossible to get any account of the number or causes of infant death outside of the households of those visited. It is worthy of note that of the 120 deaths for which causes were assigned, there were seventy-two suggestive of stomach or intestinal disease.

C. Lombroso³ in 1898 wrote:

There are pellagrous and pseudopellagrous conditions which are even harder to diagnosticate than complicated pellagra, because the pellagra, while it is present, has not been able fully to develop. Here belongs a type which I designate hereditary pellagra. It occurs in a very severe and a very mild type. It is noticeable at the end of the second year of life, rarely with desquamation, more frequently with pains in the epigastrium, pyrosis, "Heisshunger," uncertain gait, timidity, diarrhea, a yellowing of the skin as in malaria-cachexia, retardation and cessation of development; but later all symptoms of pellagra appear and resist strongly any treatment. . . . In many cases I found a bad formation of the skull, exceptional brachycephaly or dolichocephaly, fleihende (retreating?) forehead, badly set ears, asymmetry of face, anomalies of genitalia.

A complete census was taken in two mill villages. The children in every family, whenever possible, were inspected, and no difference such as Lombroso mentions could be seen between those in pellagrous homes and those in nonpellagrous homes.

In every group except Group I the ratio of adult women with children to adult women without children is about three to one. There are four sets of pellagrins, namely, adult females without children, adult males with children, girls and boys under 20, of whom the number in each group is almost the same. We have not been able to attach any significance to this equality in number. In all groups the average age of incidence in boys is 11 years, in girls 14 years, in adult females 35 years, and in adult males 52 years. The earliest age at which the disease developed was in a boy of 15 months, and the oldest was in a man of 82 years, while in women and girls the youngest was 18 months and the oldest 78 years.

2. Babcock, J. W.: A Study of Local Medical History, *Am. Jour. Insan.*, 1912, lxi, 1.

3. Lombroso, C.: *Die Lehre von der Pellagra*, p. 116.

TABLE 8.—PELLAGRINS UNDER TWENTY YEARS OF AGE, AND THE RELATIVE PROPORTION OF ADULTS WHO HAVE BORNE CHILDREN

	Groups						
	I	II	III	IV	V	VI	Total
Adult females with ehildren.....	63	45	40	27	49	21	245
Adult females without ehildren.....	10	13	15	10	16	6	70
Girls under 20 years.....	10	14	16	14	13	12	79
Total female	83	72	71	51	78	39	391
Adult males with ehildren.....	10	14	17	11	12	10	74
Adult males without ehildren.....	2	1	2	1	5	1	12
Boys under 20 years.....	10	15	12	17	15	6	75
Total male	22	30	31	29	32	17	161

TABLE 9.—ASSOCIATION OF PELLAGRINS WITH ANTECEDENT CASES

	Groups						
	I	II	III	IV	V	VI	Total.
Association outside family.....	37	19	12	7	14	8	97
Association within family.....	0	36	46	51	55	33	221
Endemic neighborhood	46	20	8	3	19	3	99
Negative history	22	27	36	19	22	12	138
Total number pellagrins.....	105	102	102	80	110	56	555

ASSOCIATION STUDY

An effort was made to find to what extent pellagrins had associated with the antecedent cases. The pellagrins studied have been grouped as follows:

1. Those who associated with pellagrins outside of the family.
2. Those who associated with pellagrins in the family.
3. Those who could give no history of association, but lived in endemic neighborhood.
4. Those who could give no history of contact.

A negative history does not mean that there had been no contact, but only that the pellagrin does not know of contact.










Table No. 9 shows positive association in 318 cases, with a possible association in the ninety-nine cases more living in endemic neighborhoods, against 138 with negative history.

CONCLUSION

An analysis of the data collected shows no evidence of direct heredity. There may, however, be an hereditary predisposition to the disease in those families in which chronic gastro-intestinal symptoms have existed for several generations. The relatively high proportion of gastric and intestinal diseases among pellagrous families would seem to substantiate this hypothesis. Of the 105 families in which there is only one case of pellagra, only three give history of intestinal or skin diseases in the ancestors, and only 1 gives history of antecedent insanity. With this predisposition to the disease, direct contact or life in endemic sections might be the exciting factor necessary for its development.

The abstracts of family histories and charts which follow will serve to show the manner of studying family groups.

The symbols used in the charts are the following:

-  Square indicates male,
-  Square with PI inside indicates male pellagrin.
-  Square with question mark inside indicates pellagra questionable.
-  Circle indicates female
-  Circle with PI inside indicates female pellagrin.
-  Diamond indicates sex unknown.
-  d. inf. indicates died in infancy.
-  Number within square or circle indicates number of children of that sex.
-  Year number under symbol indicates incidence and recurrence of pellagra.
A indicates alcoholic; B indicates blind; D indicates deaf; D M indicates deaf mute; E indicates epileptic; F indicates feeble-minded; I indicates insane; T indicates tubercular; d indicates died; P indicates paralysis.

Each horizontal line represents a generation, the symbols for the individuals of a fraternity (full brothers and sisters) being on the same horizontal line. This line is connected by a vertical line to a line joining the symbols of father and mother.

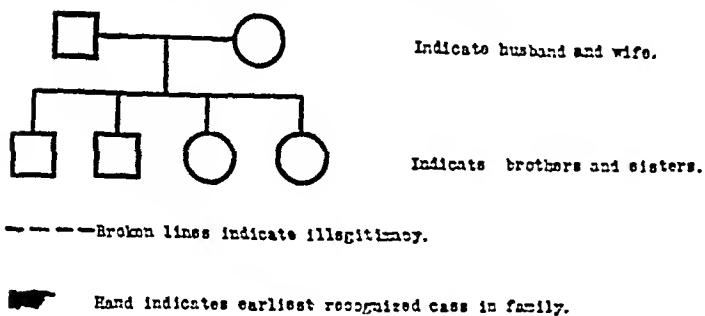


Fig. 1.—This chart gives an explanation of the symbols that are used in the succeeding illustrations of this article.

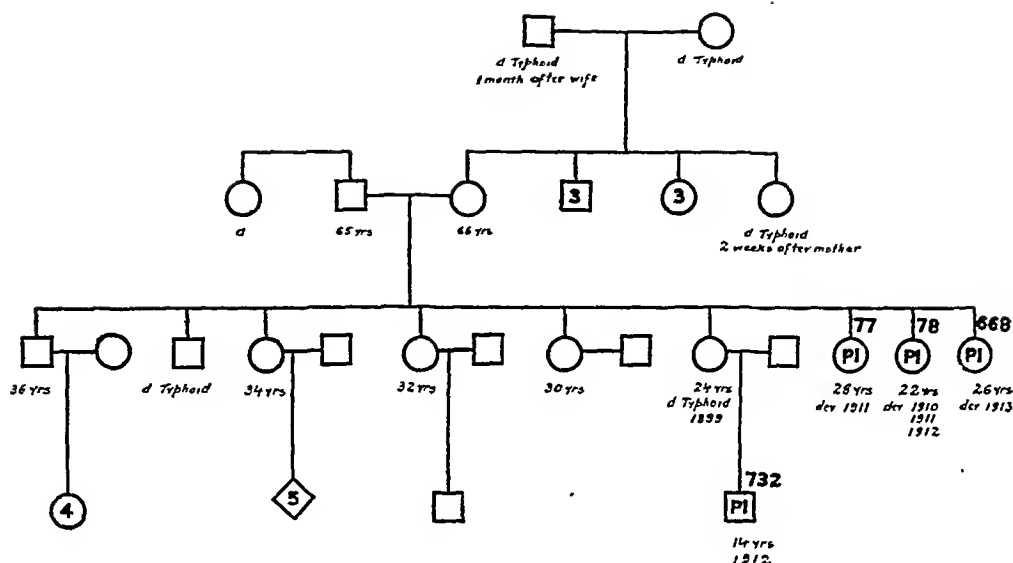


Fig. 2 (N Family).—The N family is in comfortable circumstances, two of the daughters being teachers. The first to develop pellagra was Pellagrin 78, B. N., aged 22, who clerked in a store from 1906 to 1909 and attended a "female college" from 1909 to 1911. She is now teaching. In June, 1910, pellagra developed with light erythema on hands, and in 1911 she had skin and gastrointestinal symptoms; in 1912 only skin symptoms. Pellagrin 77, G. N., aged 28, did the housework at home and slept in the same room with her sister. In the spring of 1911 she developed pellagra, which recurred in 1912, but was not present June 30, 1913, when visited.

Pellagrin 668, T. N., aged 26, a teacher, developed an acute attack of pellagra in 1913 at Good Samaritan Hospital, while there for a minor surgical operation. She had a very slight recurrence in 1914. The parents of these young women are living and well.

Pellagrin 732, E. S., aged 14, a nephew, lived with his aunts for six months in the winter of 1911 and developed pellagra the next year, 1912. He was not seen in 1913 or 1914 and it is not known whether he had a recurrence. His mother died in 1899 with typhoid fever. There were five deaths in this family from typhoid (see chart).

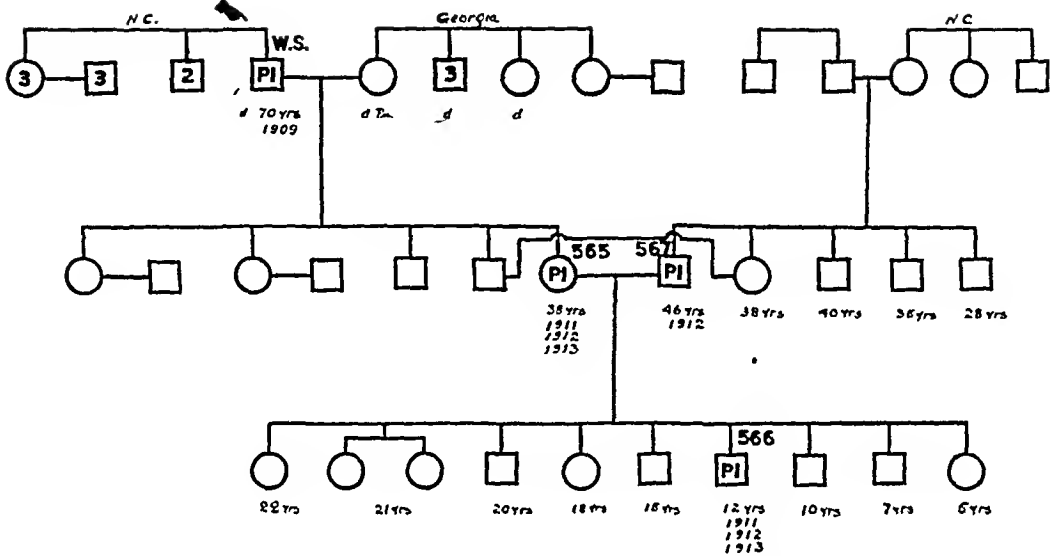


Fig. 3 (B. S. Family).—The father of Pellagrin 565, W. S., and his family lived in North Carolina. Mortality statistics were not available. W. S. died, aged 70 years, of pellagra, in North Carolina in 1909. He was nursed by his daughter, Pellagrin 565. His wife had died previously from pneumonia. Her family is in Georgia. Nothing definite could be learned concerning his illness. His daughter said that the gastro-intestinal symptoms were most pronounced, but he had also marked discoloration over hands, feet and shoulders. Three months previous to death there were marked mental symptoms.

Pellagrin 565, I. B., came with her husband to S, mill village, in 1910. She had good health until 1911. Then erythema, stomatitis and diarrhea developed. She had a typical recurrence in 1912 and very slight recurrence in 1913. Her husband, Pellagrin 567, W. F. B., aged 46 years, a mill worker, developed the disease in 1912. He did not show any recurrence of the erythema, but for four months in 1912 his other symptoms were quite severe. He had always lived in North Carolina, and his family is still there and are not known to have any disease. His father and mother and his aunts and uncles are all living and well.

They have ten children, ranging in ages from 22 years to 5 years. Only one showed pellagra, Pellagrin 566, H. B., who developed it the same time his mother did, and had recurrences in 1912 and 1913. He seemed to be as well as the other children previous to the attack.

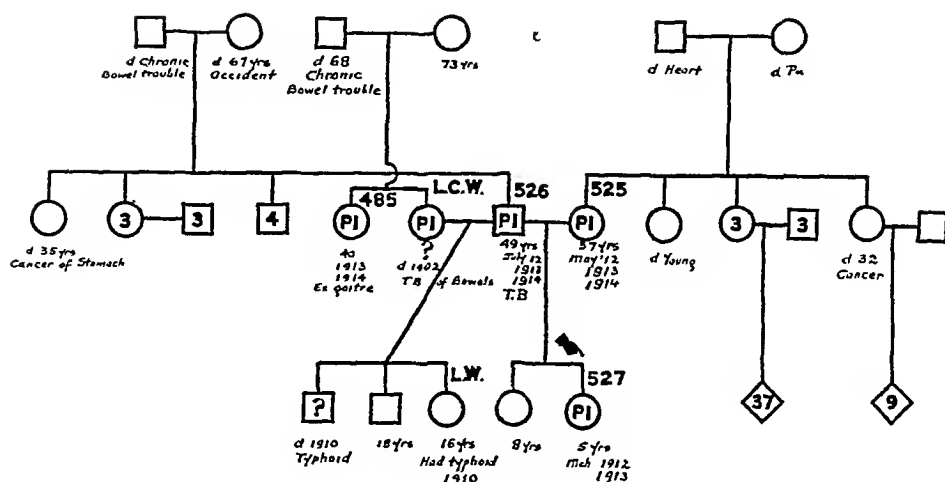


Fig. 4 (Wl. Family).—L. C. W., the first wife of Pellagrini 526, died in 1902 of tuberculosis of the bowels. Since pellagra has been recognized, the family thinks the cause of death was pellagra instead of tuberculosis. She left three children, one of whom, L. W., had typhoid fever May 28, and died in November, 1910. His symptoms were very similar to those of pellagra. One daughter, L. W., had typhoid (?) at the same time, but recovered in two months. One son, aged 18 years, is living and well.

Pellagrini 485, S. C., aged 40 years, sister of L. C. W., developed a well-marked case of pellagra in 1913. She had marked nervous and mental symptoms. There was no recurrence of erythema in 1914, but there was great nervousness and weakness. As she has exophtalmic goitre in a pronounced form, these symptoms may be due to that condition. Her mother is living and well, but her father died several years ago with chronic bowel trouble. There has been and is close association between this family and the family of Pellagrini 526.

Pellagrini 527, E. W., aged 5 years, daughter of second wife of Pellagrini 526, had whooping-cough in January and February, 1912, and in March, before she recovered, had a well-developed attack of pellagra. There was a slight recurrence of symptoms in 1913; no recurrence in 1914. Her sister, 8 years of age, shows no symptoms.

Pellagrini 525, B. W., second wife of Pellagrini 526, aged 37 years, had typhoid in 1892 and dysentery for several years following, in the summer. In May, 1912, she developed a typical case of pellagra with erythema, diarrhea and great weakness. The diarrhea continued through the winter. There were recurrences in 1913 and 1914. Her general health is improving, however. There is no history of any bowel trouble in her family. Her father died with heart trouble and her mother with pneumonia. One sister died young, cause unknown, and one married sister died, aged 32 years, with cancer of stomach. She fell and injured herself and the cancer is supposed to have resulted from the injury.

Pellagrini 526, C. J. W., aged 49 years, developed pellagra in July, 1912, and had recurrences in 1913 and 1914. He was also tubercular and became very much emaciated and excessively weak. He was in hospital for treatment in 1913; much improved in 1914. One of his sisters died, aged 35 years, of cancer. She was paralyzed at 5 years and used a wheeled chair for 30 years. The father of Pellagrini 526 died with chronic bowel trouble and his mother was thrown from a carriage when 67 years old and died from result of injury.

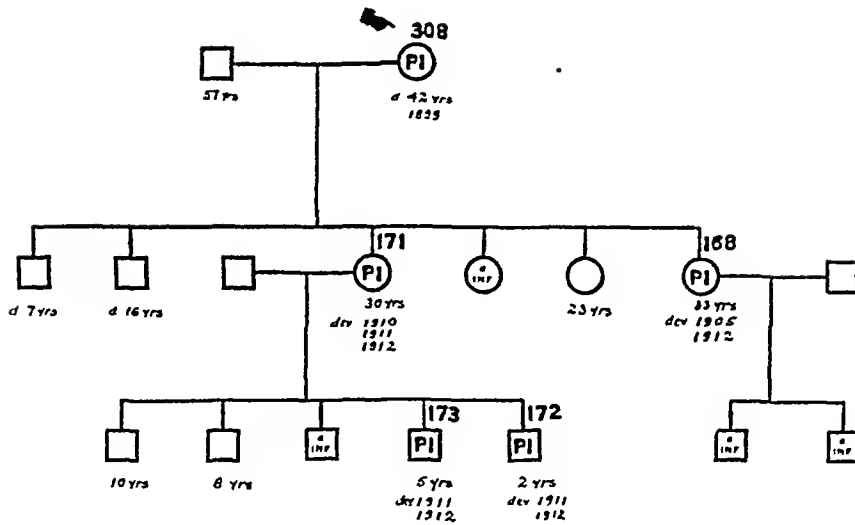


Fig. 5 (J. Family).—Pellagrin 308, E. D., mother of Pellagrin 168, died, aged 42, in 1899, on a farm in Spartanburg County. She had been in bad health for twenty years, and had skin lesions for seven years before death. She had scaling of skin of hands and severe bowel trouble. Her mind failed two years before death. The doctor who attended her thinks she undoubtedly had pellagra. The father of Pellagrin 168 is still living, aged 57 years. No one in his family is known to have pellagra. There were six children. Two boys died young—causes unknown. One daughter died in infancy; one unmarried daughter is living, apparently normal. The two remaining daughters are pellagrins.

Pellagrin 168, C. J., aged 33, worked in the mill, but for the last eight years has done housework. She cared for her mother in her last illness. All three sisters were at home during this time. Pellagrin 168 had typhoid fourteen years ago, the year following her mother's death. In June, 1905, the first typical pellagra symptoms were noticed. There has been a recurrence every year, but symptoms were most severe in 1911 and 1912. She had two sons, who died when a few weeks old; no other children. Her sister, Pellagrin 171, B. J., aged 30 years, had a bad attack of dysentery eight years ago, after the second child was born. She has not been strong since. In March, 1910, she lost her baby; did not gain health afterward; in October of the same year showed typical skin and intestinal symptoms; had recurrence in 1911 and 1912. Her husband's family is said to be free from pellagra. They had five children: two sons, aged 10 and 8 years, living and well; one son died in infancy. Pellagrin 173, W. J., had severe illness when 21 months old. He had spasms and does not talk well. His first pellagra symptoms, erythema and diarrhea, appeared in July, 1911, with recurrence in June, 1912. Pellagrin 172, A. J., was 15 months old when he showed typical symptoms in June, 1911; had a very light attack with recurrence in 1912.

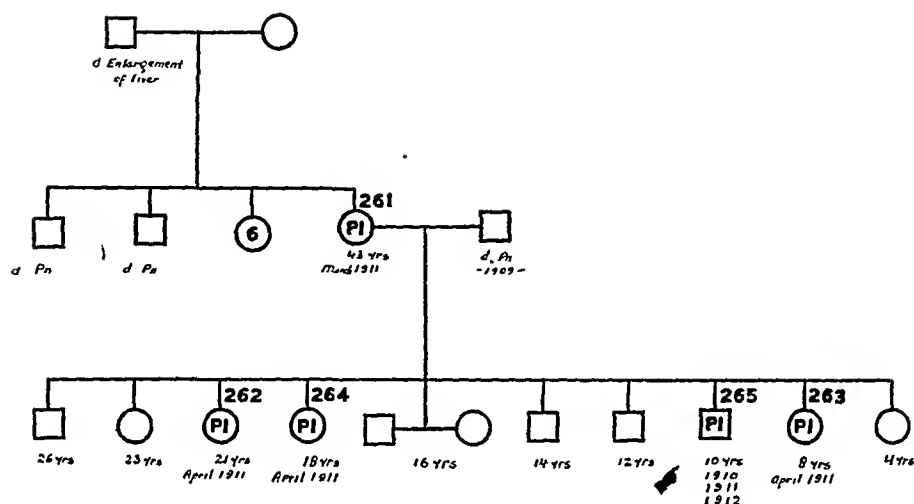


Fig. 6 (Sc. Family).—Pellagrin 261, Mrs. J. S., came originally from Tennessee, where her family all live now. Her father died of enlargement of liver, and her mother and six sisters are still living. Two brothers died of pneumonia. Her husband, Q. S., died in 1909 in Oklahoma, of pneumonia. After his death she came to South Carolina and settled in mill village B, where her son, Pellagrin 265, F. S., aged 10 years, developed pellagra in 1910. He had a marked erythema of hands, feet and legs. In 1911 there was a recurrence of erythema and dysentery. Pellagrin 261, the mother, was the next in the family to develop the disease, March, 1911. She was born in 1870, had typhoid many years ago, and malaria three years ago. In March, 1911, she had typical erythema of hands and forearms followed by stomatitis, diarrhea and general weakness. There were no definite symptoms in 1912, but she was not well during the summer. Every year since 1911 she has had diarrhea and weakness. Her mind seems dull; she is listless and stupid. It is difficult to tell whether this is the result of disease or habit.

In April, 1911, three other children, Pellagrins 262, 263 and 264 all developed pellagra. Pellagrin 262, M. S., aged 21 years, had erythema of hands and arms which lasted four months. There was no recurrence in 1912. In 1913 her hands were very red during May and June, but it was attributed to sunburn, although she works in the mill all day. Pellagrin 263, H. S., aged 8 years, had erythema of hands and feet, with severe stomatitis and diarrhea. There was a recurrence in 1912; not present in 1913. Pellagrin 264, M. S., aged 18, had simply erythema of hands and arms without other symptoms. This recurred in 1912, but was not present in 1913. There are four sons and three daughters ranging from 26 years to 4 years, not affected.

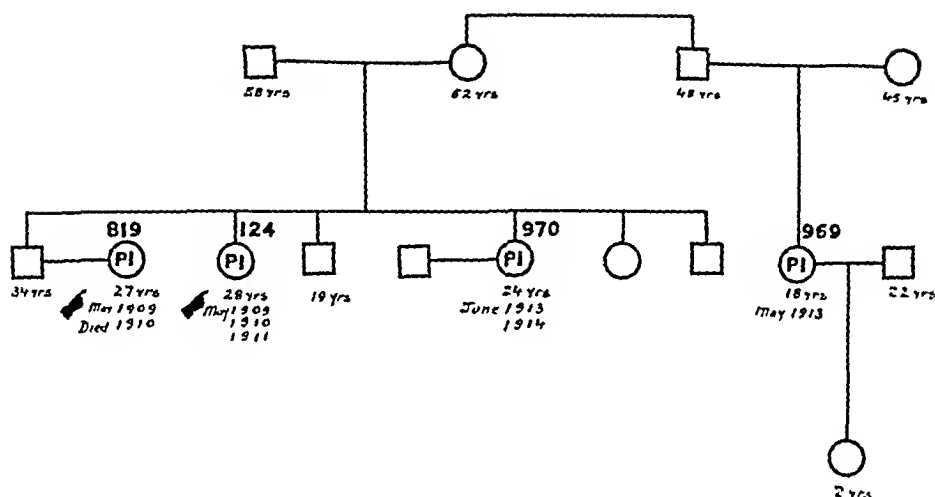


Fig. 7 (T. H. Family).—This family lived in one of the most insanitary mill villages visited. There has been much pellagra there in the last ten years, and there was an outbreak of it in 1909. The father and mother are living, strong and sturdy. They had six children, two of them pellagrins. The wife of one of the sons was also a pellagrin.

Pellagrin 124, O. T., aged 28 years, and her sister-in-law, Pellagrin 819, aged 27 years, developed pellagra about the same time, May, 1909. Pellagrin 819 lost strength rapidly and died in 1910. There were no children. Pellagrin 124, O. T., lived at home, and although she slept with a younger sister, the latter did not contract the disease. She had erythema, stomatitis and later developed diarrhea and dysentery. There were recurrences in May, 1910, and June, 1911, but there has been no recurrence since. In June, 1913, her sister, Pellagrin 970, M. H., also developed the disease. She had married and left home. She had a recurrence in June, 1914. Her cousin, Pellagrin 969, Mrs. J. L., aged 19 years, living near, and next door to a pellagrin, also developed the disease in May, 1913. She has a child 2 years old, not affected.

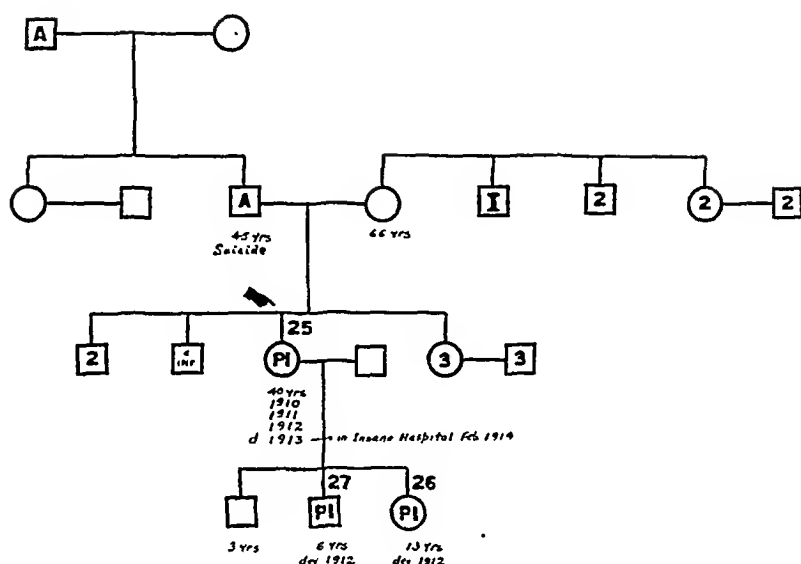


Fig. 8 (G. Family).—Pellagrin 25, J. G., born in 1872 in Georgia, married in 1897. She worked in a mill until 1906; then did housework. In 1908 she had hookworm disease followed by nervous exhaustion and physical debility. She was in the insane hospital when pellagra developed, April, 1910. She recovered sufficiently to go home; had a second attack from May to July, 1911, and a third attack in June, 1912. Her mental condition grew progressively worse, until, after a fourth attack in June, 1913, she was taken to the insane hospital, where she died in February, 1914. She had three children, two of whom were pellagrins. Pellagrin 26, E. G., born in Georgia in 1899, was a healthy child, well developed. In June, 1912, she showed skin and intestinal symptoms of pellagra. Pellagrin 27, C. G., born in 1906 in Georgia, developed pellagra about the same time. These children did not have a recurrence in 1913. They were not seen in 1914. They are now living out of the county. The father of Pellagrin 25 was alcoholic and committed suicide when 45 years of age. The paternal grandfather was also alcoholic. The mother, aged 66, is well and strong and nursed Pellagrin 25 when her mental condition was bad. Two maternal aunts and two maternal uncles are normal. One maternal uncle is insane (manic depressive?). He is in the hospital off and on. They live in Georgia—information meager. None of these relatives are known to have pellagra.

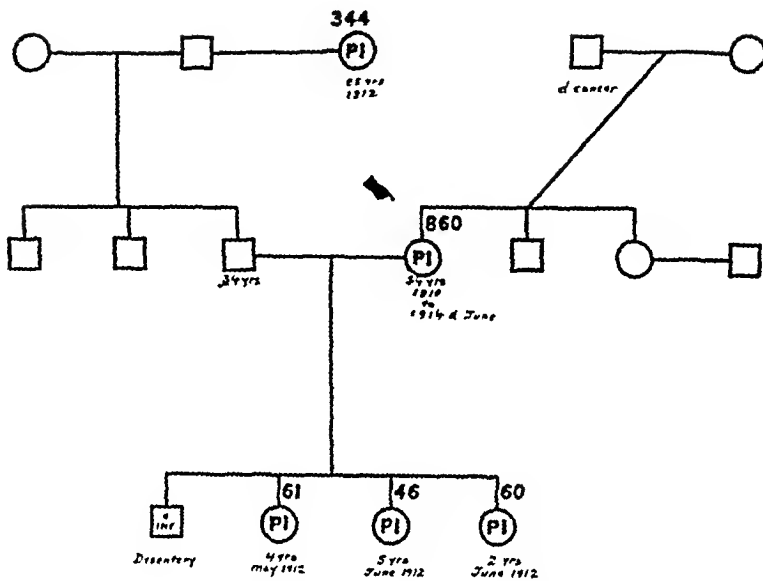


Fig. 9 (Q. Family).—Pellagrin 860, L. Q. S., aged 34 years, was a millworker in S mill village. She developed a typical case of pellagra in 1910, with a slight recurrence each year until June, 1914, when she died. These attacks were not severe enough to interfere with her work at the mill until late in the fall of 1913. Nothing could be learned of her family—she was even reticent concerning her own symptoms. Her husband is living and well. His father died of cancer.

They had four children. One boy died in infancy of dysentery. The three girls are all pellagrins. After they left North Carolina the family came to S mill village into an endemic neighborhood, a severe case of pellagra living three doors away. Pellagrin 61, L. S., aged 4 years, showed first symptoms May 1, 1912. In June of the same year both sisters, Pellagrin 46, aged 6 years, and Pellagrin 60, E. S., aged 8 years, showed typical symptoms. There was no recurrence in 1913 or in 1914.

Late in the summer of 1912 Pellagrin 344, Mrs. A. S., the children's step-grandmother, who lives with them, developed suspicious symptoms, having severe dysentery and discoloration of skin and peeling. She cared for them while parents were in the mill. In 1913 she was improving and denied having had pellagra.

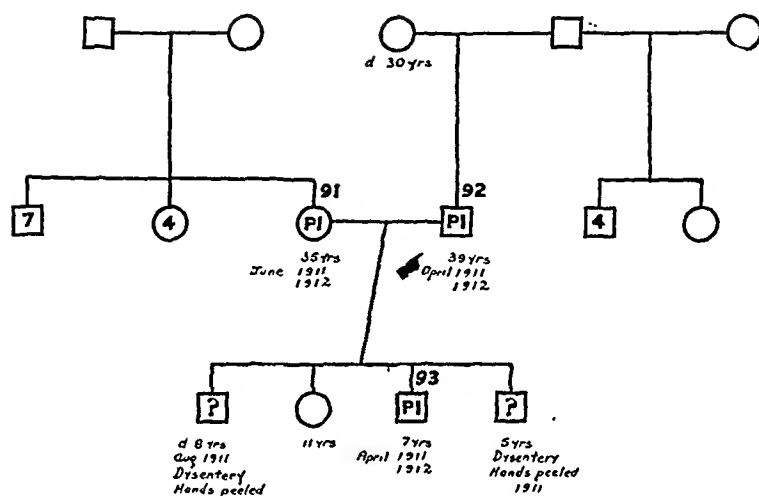


Fig. 10 (Cd. Family).—The Cd. family lived next door to a pellagrin. Mr. J. C., Pellagrin 92, aged 39 years, was a store-keeper from 1909 to 1911 in an endemic center of D mill village. Later he worked in the mill. Late in April, 1911, he developed a well-marked case of pellagra. He had a definite recurrence in 1912. His son, Pellagrin 93, F. C., had developed the disease early in the same month, and he also had a recurrence in 1912. There were three other children. The oldest, a girl 11 years of age, has never shown any symptoms, but both boys are uncertain. A boy, aged 8 years, died in 1911 with dysentery. His hands peeled; and a younger brother, aged 5 years, who is living, also had dysentery and peeling of the hands the same year. These two were reported by the mother in 1912.

The mother took care of the children, and in June she also developed the disease. She had a recurrence in 1912. Her mother, father, seven brothers and four sisters have never shown any symptoms of pellagra.

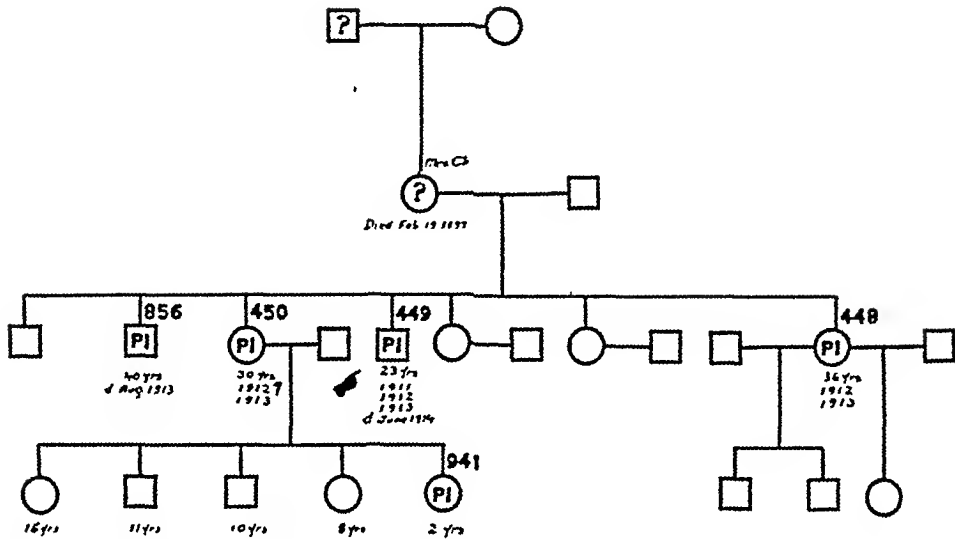


Fig. 11 (Ch. Family).—The maternal grandfather of the Ch. family is said to have died with symptoms resembling pellagra in October, 1896. He lived on a farm in North Carolina, twenty-five miles from his daughter's family. The mother, Mrs. Ch., had recurrent spring attacks of stomatitis, bowel trouble and breaking out of hands and face. Her mind was affected toward the last. She was sick about four years and died Feb. 19, 1897. All the children were living at home while she was sick. Four of them have since developed pellagra. Pellagrin 449, R. C., aged 23, developed pellagra in 1911 or 1912 in Kentucky or North Carolina. In 1913 he visited his sister, Pellagrin 450. He was in a run-down condition, but secured work in the mill and remained with his sister through 1913 and 1914. He grew gradually worse and died in the City Hospital in June, 1914. His sister, Pellagrin 450, aged 30, has had sore mouth and stomatitis for six or seven years. Pellagra was not recognized, however, until 1912. Her hands peeled definitely in 1913. There was no recurrence in 1914.

She has five children, none affected except the youngest, Pellagrin 941, C. C., aged 2 years. She developed gastro-intestinal trouble in January, 1913, and showed her first erythema in May, 1914. She was very fond of her Uncle Bob, Pellagrin 449, and slept with him even after he was confined to bed. They used a common drinking cup. Pellagrin 448, F. D., aged 36, developed pellagra while living in Kentucky in 1912. She later came to a mill village near S; had a recurrence in 1914. Pellagrin 856, H. C., aged 40 years, has had bowel and stomach trouble every spring for three years. He visited in the homes of Pellagrin 448 and Pellagrin 449, staying some nights with one and some with the other. He has been insane since 1912. No erythema was noticed until June, 1913. He died in August, 1913, in North Carolina.

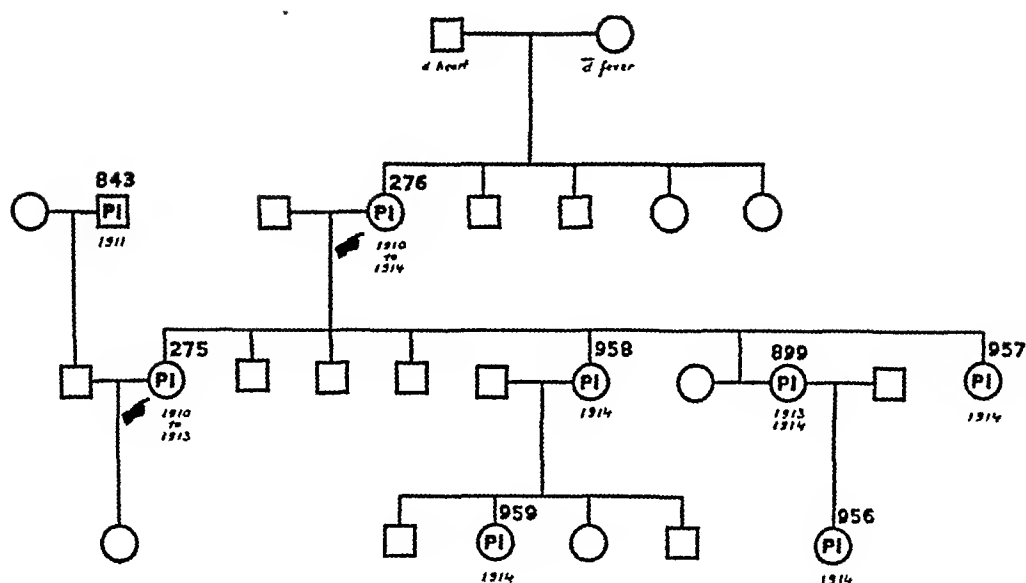


Fig. 13 (W. Family).—In the spring of 1910 Pellagrins 276, Mrs. M. W., and Pellagrins 275, Mrs. E. W., mother and daughter, developed pellagra about the same time. They were both in good physical condition, but Pellagrins 276 gave a history of dysentery in the summer for three years prior to 1910. They had both visited Pellagrins 352 and 825, cases with very severe symptoms. The mother, Pellagrins 276, aged 50 years, had recurrences in 1911, 1912, 1913 and 1914. There has been severe mental disturbance from the beginning of the disease, and when seen in June, 1914, her mind was almost a blank. She was greatly emaciated and a great care to her family. Her ancestors and fraternity are negative to pellagra. Of eight children, four are pellagrins; she has also two pellagrous grandchildren. This family lived in mill village A from 1910 to 1912, when they moved to the country and remained there until June, 1913. They then returned to mill village A and moved into a house just vacated by a pellagrins.

Pellagrins 275, Mrs. E. W., aged 22 years, who developed the disease the same year her mother did, had recurrences in 1911, 1912 and 1913, with a slight return of stomatitis and erythema Aug. 1, 1914. Pellagrins 843, Mr. M. W., father-in-law of Pellagrins 275, was a frequent visitor at his son's house. In 1911 he had a sharp and severe attack of pellagra, but there has been no definite recurrence. In August, 1913, Pellagrins 899, Mrs. W. W. L., another daughter of Pellagrins 276, had all the typical symptoms of pellagra, which recurred with lessened severity in May, 1914. Her daughter, Pellagrins 956, R. L., aged 4 years, developed pellagra in May, 1914. Pellagrins 957, A. W., another daughter of Pellagrins 276, aged 18 years, developed pellagra in February, 1914, and her hands were peeling when Pellagrins 959 developed the disease. Pellagrins 958, Mrs. M. W. P., another married daughter of Pellagrins 276, living next door, aged 23 years, developed the disease in February, 1914, and the gastro-intestinal symptoms were still present in August, 1914. She was a daily visitor at her mother's home. In March, 1914, Pellagrins 959, I. P., daughter of 958, aged 6 years, developed the disease. When seen this child was on the bed by the grandmother, and it is certain that the association was very close in all of these cases.

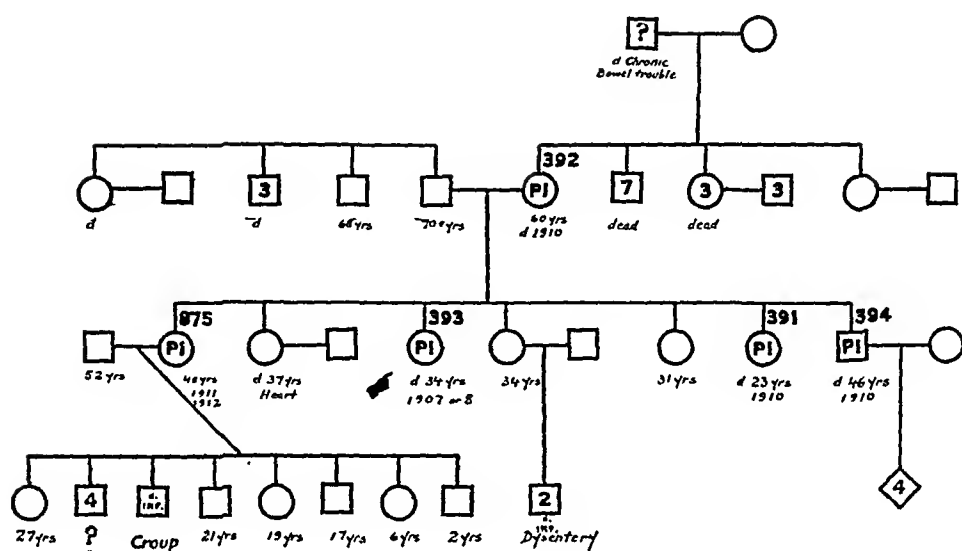


Fig. 14 (H. L. Family).—The first authentic case in the family is Pellagrin 393, M. H., aged 34 years. Hers was one of the early cases of pellagra in Spartanburg County, and she died either in 1907 or 1908. Her mother, Pellagrin 392, A. B. H., aged 60 years, had suffered for several years with chronic bowel trouble and recurrent erythema. She had a stroke of paralysis in 1908. She lost strength rapidly and died in 1910, after being helpless nearly two years. She had seven brothers and three sisters, all dead. None of them were known to have had any signs of pellagra. Her husband, F. A. H., is still living, over 70 years of age. He has one brother living and well. The rest of his family are dead.

There were seven children, four of whom had pellagra. One daughter died at the age of 37 years with heart trouble. One daughter, living and well, lost both her boys in infancy with dysentery. The only son, Pellagrin 394, J. H., aged 40 years, died with pellagra in August, 1910, the same year his mother and sister died. Pellagrin 391, E. H., aged 23 years, died in the State Hospital for the Insane May 15, 1910.

The following year another sister, Pellagrin 875, M. L., aged 45, had severe erythema and gastro-intestinal symptoms, with a recurrence in 1912. Her husband is living and well and there is no history of pellagra in his family. They had six living children ranging in ages from 27 to 2 years, not affected. Five children died in infancy.

It is questionable whether the father of Pellagrin 392 did not die with pellagra. He died with chronic bowel trouble, and the neighbors say he had erythema and mental derangement before death.

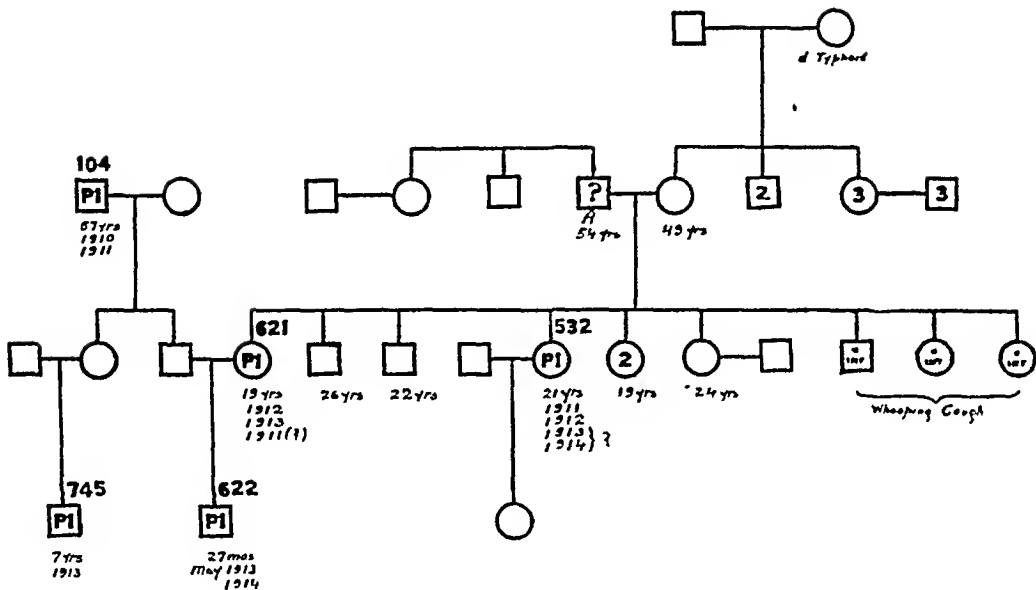


Fig. 15 (P. W. Family).—Pellagrins 104, N. P., aged 57 years, a mill operative, was in good physical condition until the spring of 1910, when he developed a severe case of pellagra. He had severe gastro-intestinal symptoms, stomatitis and erythema. He soon became prostrated and was obliged to give up his work. His wife was afraid that she would contract the disease, so it was necessary for him to visit around among his relatives to get the necessary care. He spent much time with Pellagrins 621, a daughter-in-law, and with his daughter, the mother of Pellagrins 745. He became a little better in the winter, but in the spring of 1911 he had a recurrence. No history of his antecedents was obtainable.

Pellagrins 621, B. P., aged 19 years, waited on her father-in-law in 1910. In 1911 her hands and arms peeled, and it was thought she had pellagra, but no other symptoms developed, and the diagnosis was questionable until 1912, when she had a recurrence with stomatitis and erythema. There was also a recurrence in 1913. In 1914 she was working in the mill, having separated from her husband. She and her son were living at her father's. Her son, Pellagrins 260, H. P., 27 months old, developed pellagra in 1913. When seen in 1914 there was a very slight erythema on the hands and forearms and a slight diarrhea.

In 1911 Pellagrins 532, Mrs. A. B., aged 21 years, sister of Pellagrins 621, developed a well-marked case of pellagra. She lost weight and became apathetic and depressed. She had recurrences in 1912 and 1913, but the symptoms were more mental than physical. She has a daughter not affected. She and her sister visited frequently, and in addition to this, she lived next door to a pellagrins, their water-closets adjoining. Pellagrins 621 and Pellagrins 532 have two brothers and three sisters, never affected. One brother and two sisters died in infancy with whooping-cough. Their father is alcoholic. He is living, aged 54 years, in the country near one of the mill villages in which pellagra is endemic. He had some vague symptoms which the family thought might be pellagra, but the diagnosis was not confirmed. The mother is living and well. Her family, two brothers and three sisters, are negative to pellagra.

Pellagrins 104 has had no recurrence of pellagra since 1911. He still visits around, spending much time with his daughter. Her son, Pellagrins 745, P. C., aged 7 years, is very fond of his grandfather and is with him constantly when opportunity offers. In 1913 he developed a well-defined case of pellagra.

(Query: If pellagra is a germ disease, in what way can it be carried from one person to another? Can a person be a carrier of the disease after he is apparently well?)

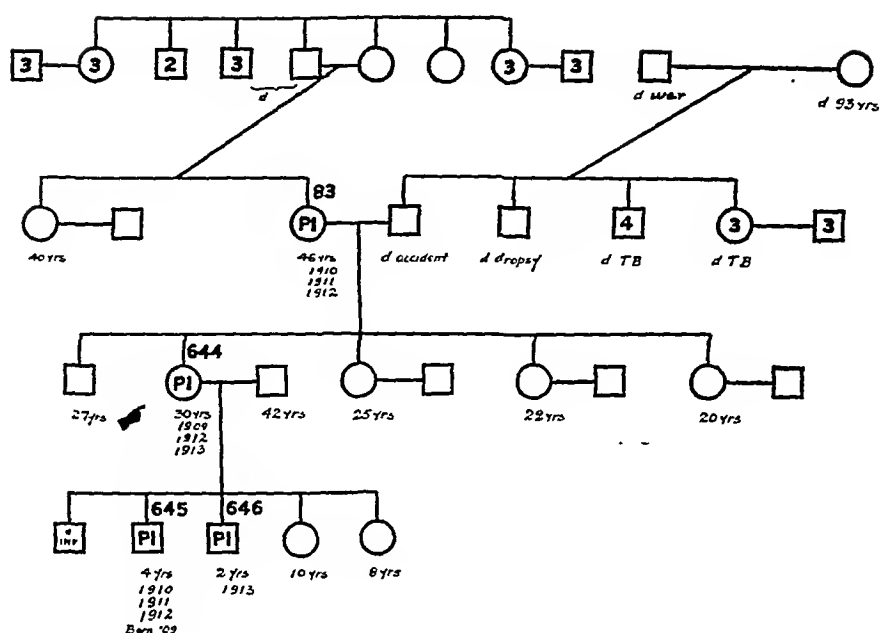


Fig. 16 (F. S. Family).—Pellagrin 83, I. F., 46 years of age, was born in North Carolina. She had typhoid fever twenty-one years ago, since which time her general health has been good. She developed pellagra in June, 1910, while living in W mill village. It recurred in August, 1911, and again in 1912. No details could be obtained of her ancestors except that her father and three uncles died in the war, and the others are living in North Carolina; no history of pellagra in any of them. She has one sister, 40 years of age. Her husband, A. F., died of an accident to his head. His family all died young, one brother with dropsy, four brothers and three sisters with tuberculosis.

Pellagrin 83 had five children ranging in ages from 30 years to 20 years, only one of them having pellagra. Pellagrin 644, A. S., the oldest child, born in North Carolina in 1883, had asthma and heart trouble. She moved to Spartanburg County and the first symptom of pellagra appeared in April, 1909. It was quite mild, as she was four months pregnant. Her baby was born in September, 1909. Her second attack was in 1910, but there was no erythema on the hands. The third attack occurred in 1911, but without erythema on hands; fourth attack occurred in 1912 with stomatitis; fifth attack, in 1913, mild, but with definite and typical eruption. She has lost 22 pounds in two years. She has had five children: One son died in infancy, two daughters are well, and two children born while she had pellagra have both developed the disease.

Pellagrin 645, F. S., born in September, 1909, developed pellagra in March, 1910, and has had recurrences in 1911, 1912 and 1913. Pellagrin 646, A. S., born in September, 1911, developed the disease in 1913. These children have had slight attacks of erythema with rather severe intestinal symptoms.

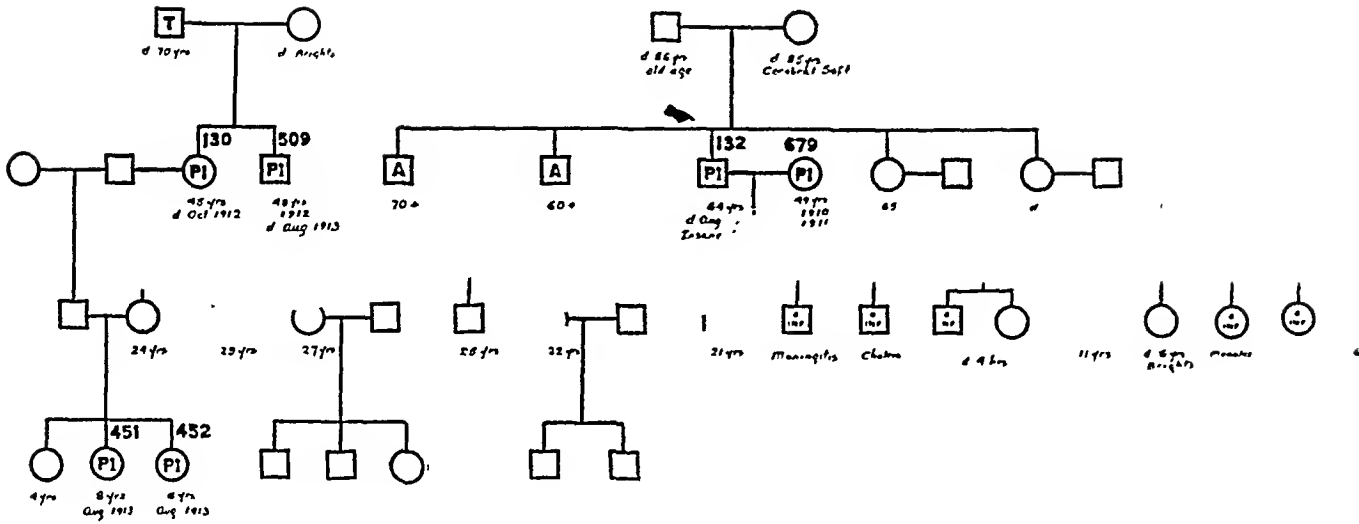


Fig. 17 (S. B. Family).—The S. B. family history is offered to show the way pellagra seems to be transmitted to others by close association. The earliest known case in this family was Pellagrin 132, Mr. J. B., aged 64 years. He was naturally a strong man, slightly but not excessively alcoholic. His digestion had been impaired for several years. He was a mill worker in mill village S and lived in an endemic area. He developed pellagra in the spring of 1909. He had marked erythema, severe diarrhea and decided mental disturbance. He grew rapidly worse and was taken to the State Hospital for the Insane, where he died in August, 1909. His wife denies that he had pellagra. She says that he had sunburn and died of cerebral softening just as his mother did. Two of his brothers, both alcoholic, are living; one sister is living, and one died a few years ago. None of them showed any pellagra symptoms. They did not live in the same section.

His wife, Pellagrin 679, Mrs. J. B., aged 49 years, took care of her husband until he went to the hospital. The next spring, 1910, she had a slight attack of pellagra without mental symptoms. She had also a recurrence in 1911. It was impossible to get her family history, as she resented questioning and even denied the presence of pellagra in herself and husband. They had fifteen children: six died in infancy, one died of Bright's disease when 6 years of age; the other eight are all living, none of them ever having shown signs of pellagra, although six of them lived at home when the mother and father had pellagra.

Two grandchildren, Pellagrin 451, A. S., aged 8 years, and Pellagrin 452, P. S., aged 6 years, developed pellagra in August, 1913. A younger sister in the same household is free from the disease. In addition to living in an endemic section and playing with affected children, these children were frequent visitors at the home of their step-grandmother, who died of pellagra the previous year. Pellagrin 130, Mrs. P. S., aged 45 years, the step-grandmother mentioned, was always visiting the sick and waiting on them. She developed pellagra in 1911 or 1912. She had very severe erythema and intestinal trouble and died in October, 1912. Her brother, Pellagrin 509, J. S., aged 48 years, visited at the home of his sister, staying over night and often eating there. In 1912 he developed pellagra, and in August, 1913, he died at the Pellagra Hospital. His skin lesions were very severe and diarrhea excessive.

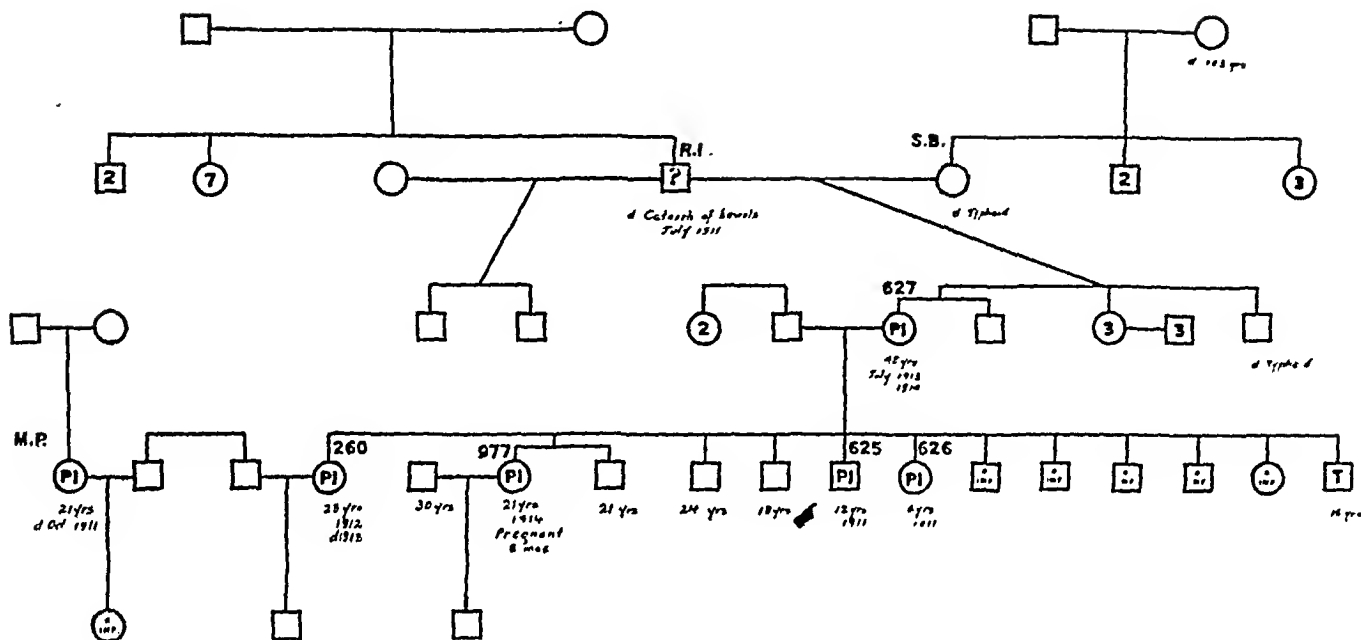


Fig. 19 (R. Family).—Pellagrin 260, S. M. P., aged 23 years, had the first case of pellagra discovered in this family. She developed it during pregnancy in 1912. She lived with her mother until the mental symptoms became marked, when she was taken to the Good Samaritan Hospital, where she died on Sept. 7, 1913. In July, 1913, the mother, Pellagrin 627, M. E. R., aged 45 years, had typical symptoms. She has eight living children. Four sons have shown no symptoms of pellagra. One son, 16 years of age, has a pronounced case of tuberculosis. There were five children who died in infancy, either being born dead or having died in a few days or hours. Two sons, D. R., Pellagrin 625, aged 12 years, and P. R., Pellagrin 626, aged 6 years, had pronounced symptoms in 1911, the same year her father died with catarrh of the bowels. In June, 1914, M. L., Pellagrin 977, visited her mother for a week. The mother returned home with her and spent two weeks. July 6, 1914, Pellagrin 977 developed the disease. As she was eight months pregnant, she was quite nervous for fear she would have it as Pellagrin 260 did.

Mrs. R., Pellagrin 627, could not remember whether her father, R. L., had skin symptoms or not. He died of catarrh of the bowels in July, 1911. He had seven sisters and two brothers, who were negative to pellagra. R. L. was married twice. By his second wife there were two sons, living and well; by his first wife there were six children. One son, B. L., died of typhoid; one daughter, Pellagrin 627, mother of Pellagrin 260, has pellagra; the others are living in South Carolina and are well. The maternal grandmother, S. B., died of typhoid. The history of her two brothers and three sisters is unknown. Her mother died at the age of 102, of old age. M. P., a sister-in-law of Pellagrin 260, living diagonally across the street from the R. family, died of pellagra in October, 1911.

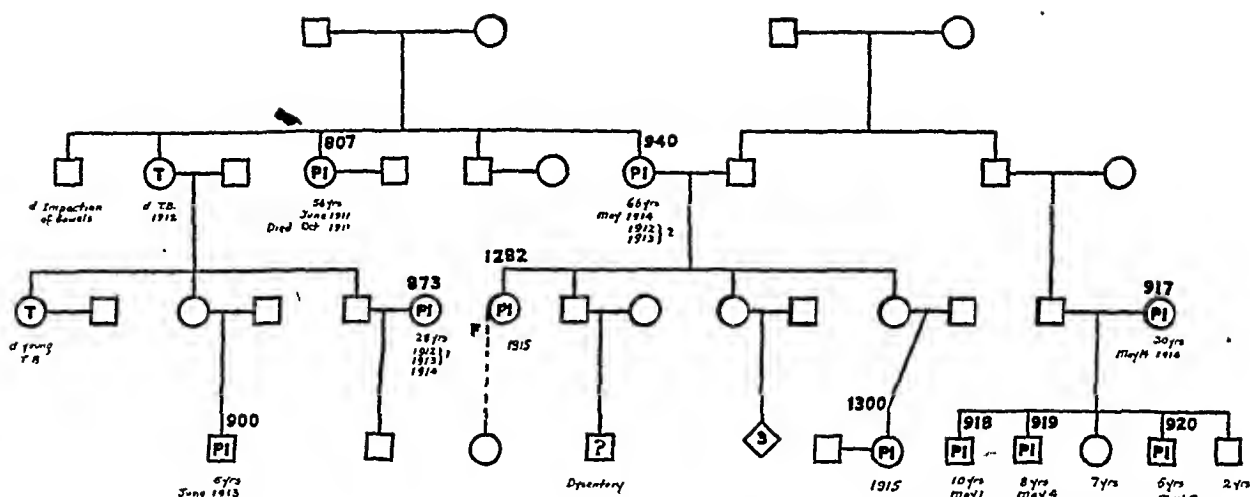


Fig. 20 (H. Family).—The pellagrins in this group are all related, but they represent three distinct families. Pellagrins 873 and 917 married into the H. family. They were, however, so intimately connected that it was impossible to consider them separately. The first member of the H. family to develop pellagra was Pellagrins 807, Mrs. F. H. M., aged 56 years. She was living in the country and no contact history could be obtained, but it is known that four other cases within a radius of one mile developed pellagra the same year. Pellagrins 807 began April, 1910, to show symptoms of indigestion followed by bowel trouble. She was sick during the summer, but in December was feeling much better. In February, 1911, she had a very severe attack of indigestion, lost weight, and in June, 1911, developed erythema on the hands and arms. She died on Oct. 11, 1911. She was cared for by her nephew's wife, Pellagrins 873. Later she was taken to her sister's, Pellagrins 940, in village A, where she died in about ten days.

Pellagrins 873, Mrs. F. H. C., niece by marriage, lived nearly opposite Pellagrins 807, and nursed her for several months. She had indefinite symptoms of pellagra in 1912 and again in 1913, insomnia, burning of the hands, weakness and dizzy feelings. The first erythema appeared in April, 1914. She now has a well-developed case of pellagra. Her husband's sister died in 1912 of tuberculosis. Another sister of the husband lives only 100 yards away, and the son of this woman, Pellagrins 900, H. C., aged 6 years, developed pellagra in June, 1913, with recurrence in June, 1914. There was a typical eruption each year. He was a constant visitor at the house of Pellagrins 873.

Pellagrins 940, F. H. B., aged 66, at whose home Pellagrins 807 died, has had indigestion and loose bowels since 1912. In May, 1914, the first erythema appeared, accompanied by weakness, loose bowels and stomatitis. When last seen, Aug. 1, 1914, she was in bed with weakness and mental symptoms. One brother of Pellagrins 940 is still living. One sister died of tuberculosis and one brother died last year of impaction of the bowels.

Pellagrins 1282, L. B., aged 29 years, living with her mother, Pellagrins 940, developed pellagra in June, 1915; other early symptoms were denied. There was slight desquamation still present when seen Aug. 6, 1915. Pellagrins 1300, M. P. W., aged 22 years, granddaughter of Pellagrins 940, developed pellagra in July, 1915, while in Danville, Va. She had been living there only three months when the disease developed. Prior to that time she had lived in mill village Sa, next door to a pellagrins, whose son she married.

Pellagrins 917, Mrs. S. B., aged 30 years, niece by marriage, lived near her aunt in an endemic area five months before pellagra developed. She had lived four years prior to this next door to a pellagrins; there was very intimate association; and the children played together. She and three of her four children, Pellagrins 918, 919 and 920, all developed definite cases in May, 1914. Pellagrins 918, A. B., the 10-year-old son, was the first to show symptoms, the others following in quick succession.

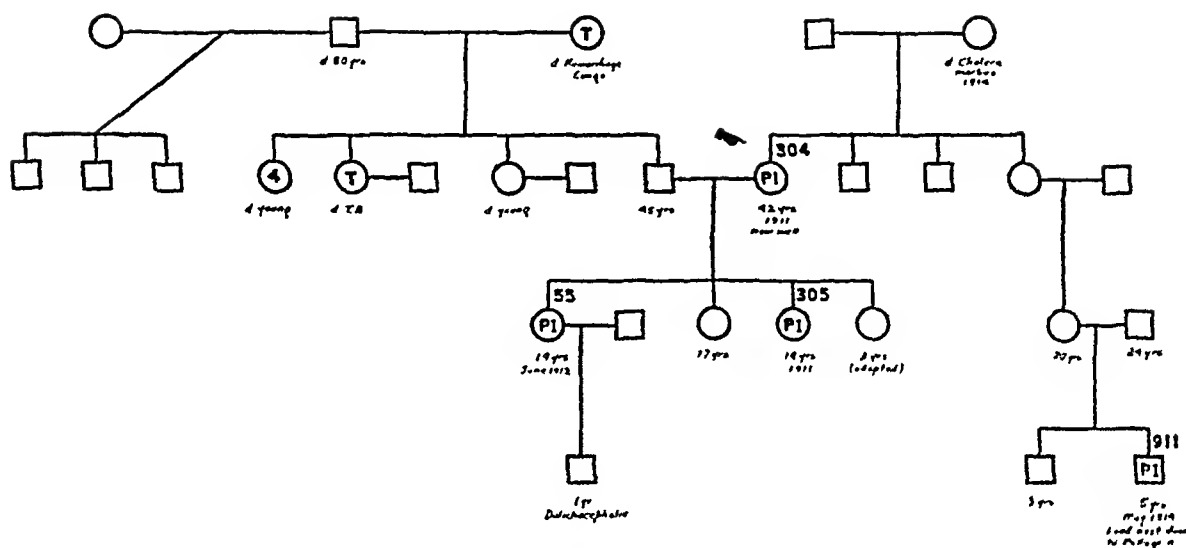


Fig. 21 (P. Family).—The maternal grandmother died in 1904 with cholera morbus. The father's family was tubercular. The mother, Pellagrin 304, Mrs. J. P., aged 42 years, developed pellagra in mill village S, an endemic center. She had no recurrence in 1912 and 1913. Her daughter, Pellagrin 305, Miss O. P., aged 14, had active symptoms the same year. Another daughter, Mrs. G. P. G., Pellagrin 55, aged 19, moved in March, 1912, to a house in the country formerly occupied by Pellagrin 56. In June, 1912, she developed pellagra. She had been closely associated with her mother and sister, and had lived in several mill villages where pellagra existed. When seen in 1913 there were no active symptoms, but she was very weak and had digestive trouble; was pregnant. Her son, 1 year old, has had chronic bowel trouble all his life. He is dolichocephalic.

In May, 1914, Pellagrin 911, J. B., aged 5 years, the son of a cousin of Pellagrin 55, developed pellagra. The family had been living from December, 1913, to February, 1914 in a house next door to Pellagrin 133.

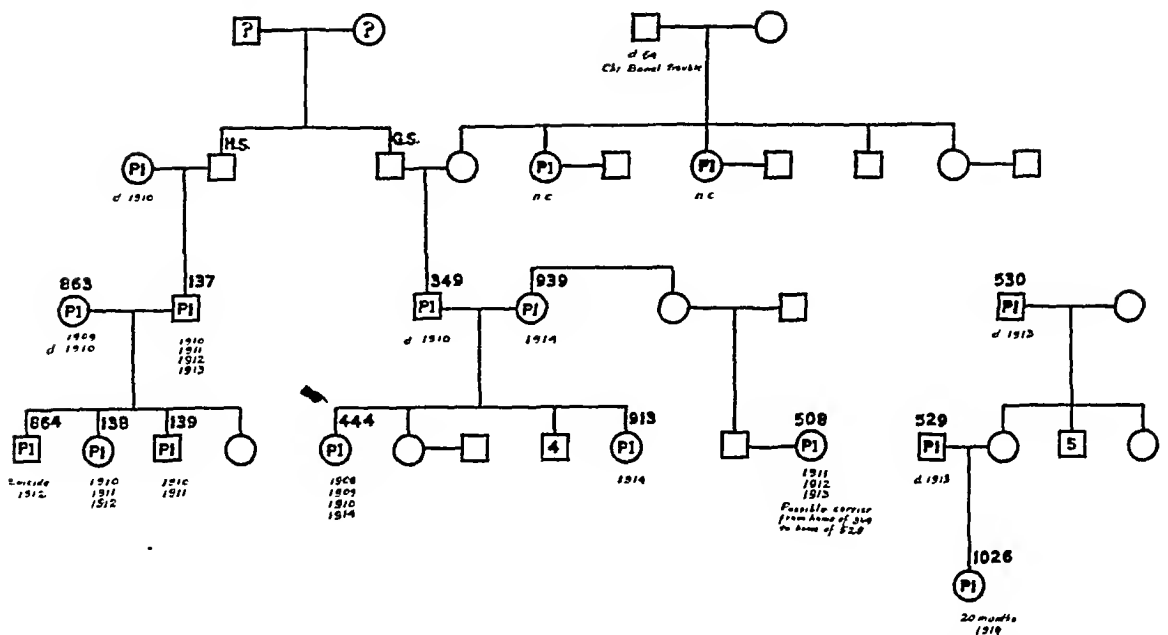


Fig. 22 (S. Family).—The paternal grandfather of Pellagrins 137 and Pellagrins 349 lived and died in Spartanburg County; cause of death unknown. He had two sons, H. S. and G. S. H. S. married M. C., who died in 1910 with pellagra. She had not been well for two years prior to the development of the disease. Their son, Pellagrins 137, Mr. J. S., developed pellagra the year his mother died. At that time he was living on a farm not in an endemic section, but visited his mother frequently, and she also paid long visits to him. In 1907 he began to have chronic dysentery and indigestion, and in 1908 had a severe and prolonged attack of malaria. His digestion became more impaired and in 1910 he had typical erythema accompanied by gastro-intestinal symptoms and mental disturbance. In June he went to the Columbia State Hospital for treatment and remained there six weeks. Symptoms subsided and he returned home. There were recurrences in 1911, 1912 and very slightly in 1913. His wife, Pellagrins 863, Mrs. J. S., developed pellagra in the fall of 1909. She had a very severe attack and died in April, 1910. There were four children.

Pellagrins 864, C. S., son, developed pellagra in 1911 and in 1912 developed marked mental symptoms. He tried to shoot his wife and was taken to the Columbia State Hospital, where he committed suicide. Pellagrins 138, A. L. S., daughter aged 17 years, had erythema in 1910, with recurrences in 1911 and 1912. There were no symptoms in 1913. Pellagrins 139, C. S., son aged 19 years, developed pellagra in 1910, with recurrences in 1911. There were no definite symptoms in 1912 and 1913. One daughter, 15 years of age, living in the same house, did not have the disease.

G. S., the other son, married and had a son, Pellagrins 349, G. S., aged 53 years, who developed pellagra in the spring of 1909 after caring for his daughter, Pellagrins 444. There is no history of contact with his cousin's family. Pellagrins 444, C. S., aged 10 years, developed pellagra in the spring of 1908. It recurred in 1909 and 1910. The erythema was severe, especially on the feet and legs. These were dressed by his father, Pellagrins 349, who developed the disease and died in June, 1910. Pellagrins 444, had no recurrences of the disease after 1910 until May, 1914. In June, 1914, her sister, Pellagrins 913, L. S., aged 6 years, developed it. Four brothers and one married sister living at home have not yet had the disease. In June, 1914, the mother, Pellagrins 939, Mrs. G. S., aged 42 years, developed a well-marked attack of pellagra. Their home is in an endemic section. The question arises whether there was a fresh infection in 1914, or whether Pellagrins 444 had a recurrence after three years.

It was impossible to get the history of this family on the paternal side. The maternal grandfather of Pellagrin 349 died with chronic bowel trouble. Two aunts died with pellagra.

There is an interesting connecting-link between this family and the E. family. Pellagrin 508, E. C., aged 20, lived with the family of Pellagrin 349 for one year, 1910. In 1911 she developed pellagra. She boarded with Mr. H. L., Pellagrin 529, in 1912, when she had a recurrence. From there she went to North Carolina, where she remained six months. In the spring of 1913 she returned, married a nephew of Pellagrin 939 and boarded in the vicinity, being a frequent visitor at the homes of Pellagrin 939 and Pellagrin 529. She died in May, 1913.

Pellagrin 529, with whom Pellagrin 508 boarded, Mr. H. L., aged 23, developed pellagra in March, 1913. His mental symptoms were marked from the first. He went to Tennessee, where he died in the summer of 1913. Before going to Tennessee he lived eleven weeks with his wife and baby in rooms upstairs in the home of his father-in-law, Pellagrin 530, Mr. E., who developed pellagra in May, 1913. He became rapidly worse, lost weight, and died in July, 1913. In July, 1914, T. L., daughter of Pellagrin 529, and granddaughter of Pellagrin 530 developed a typical case of pellagra, Case 1026.

This chart seems to signify heredity, but it will be noticed that there are five distinct families represented by pellagrins, and in every instance except the case of the mother of Pellagrin 137 and the case of Pellagrin 444 there is a history of close contact.

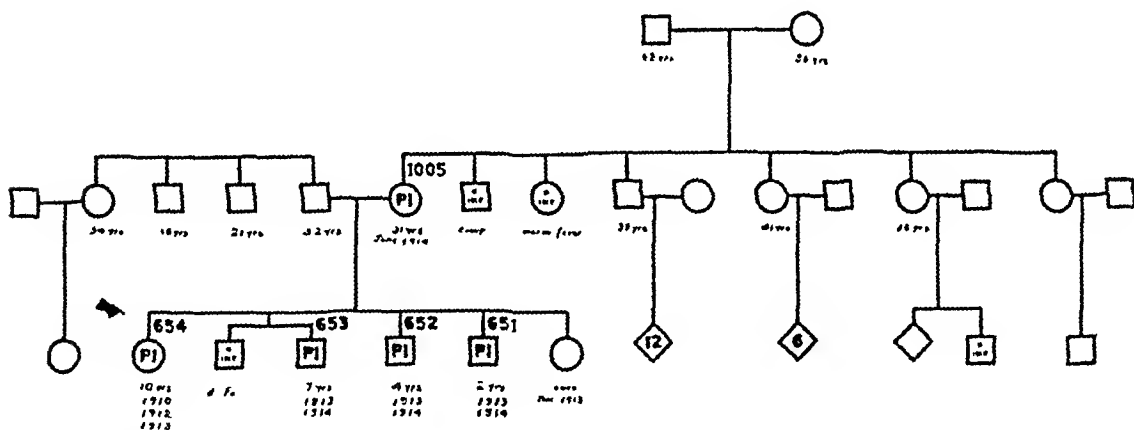


Fig. 23 (F. Family).—The first member of the F. family to develop pellagra was Pellagrin 654, B. F., aged 10 years, a school girl. She had typhoid when 2 years of age, but recovered and was apparently in good physical condition in 1910, when the first symptoms appeared. There were recurrences in 1912 and 1913, but in 1914 she seemed perfectly well. In June, 1913, the three remaining children, Pellagrin 653, P. F., aged 7 years, Pellagrin 652, C. F., aged 4 years, and Pellagrin 651, T. C. F., aged 2 years, all had severe bowel trouble and showed the typical skin lesions. Each of these three children had a recurrence in May, 1914. R. F., born November, 1913, had not developed pellagra.

Pellagrin 1005, N. P. F., the mother, also has the disease. She developed it in June, 1914. There is no known physical defect in her family. Her father and mother are living and well, and she has two brothers, three sisters and twenty nieces and nephews, who have never had pellagra. One brother died in infancy of "worm-fever." She lost one son, the twin brother of Pellagrin 653, when 21 months old, with pneumonia.

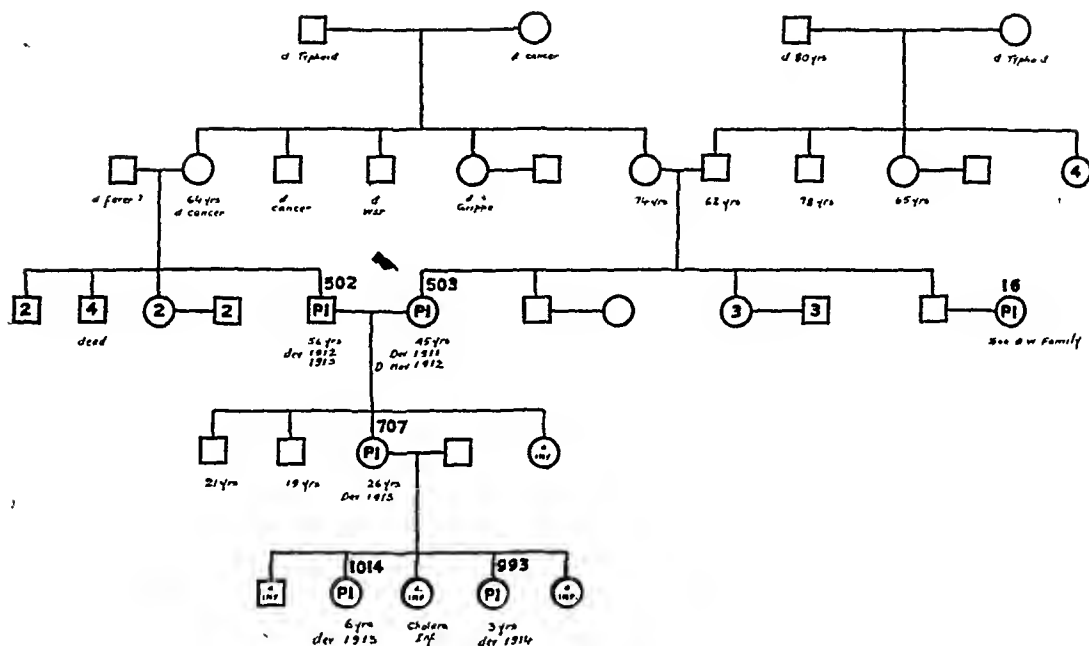


Fig. 24 (B. R. Family).—The first member of this family to have pellagra was Pellagrin 503, although her brother's wife, Pellagrin 16, had it three years earlier. It is not known whether there was close association or not. Pellagrin 503, F. B. R., aged 45 years, was always a hard worker at housework exclusively. She developed pellagra in May or June, 1911; she seemed to get better during the winter, but had a recurrence in 1912, with marked mental symptoms. She died in November. She visited frequently Pellagrin 110. Her husband, Pellagrin 502, W. R., aged 56, born on a farm near Columbia in 1857, was a farmer all his life. His general health was good. In 1912 he began to have trouble with his digestion, and early in November, 1912, he developed typical symptoms of pellagra. These recurred in 1913, but in 1914 there were no marked symptoms though there was a general weakness. In addition to living with his wife, he was a frequent visitor at the homes of Pellagrins 110, 130 and 17. They had four children: one died in infancy; two sons were not affected, and a daughter, Pellagrin 707, M. C., 26 years of age, who had a typical attack of pellagra in the summer of 1913, was a constant visitor at her mother's home and after the mother's death lived with her father. She is married and has had five children. Three died in infancy, one with cholera infantum and one teething. Two are pellagrins. Pellagrin 1014, M. C., 6 years of age, developed the disease in 1913. She lived most of the time with her grandmother, often sleeping with her. Pellagrin 993, K. C., aged 3 years, developed pellagra in 1914. Hygiene and sanitation were practically unknown in this family.

The mothers of Pellagrin 502 and Pellagrin 503 were sisters. The mother of Pellagrin 502 died with cancer; her brother and mother died with the same disease. The mother of Pellagrin 503 is still living, aged 74 years, strong and healthy. The father of Pellagrin 503 is also living. They are better-class mill people, and are in very comfortable circumstances. The father's mother and the mother's father died of typhoid.

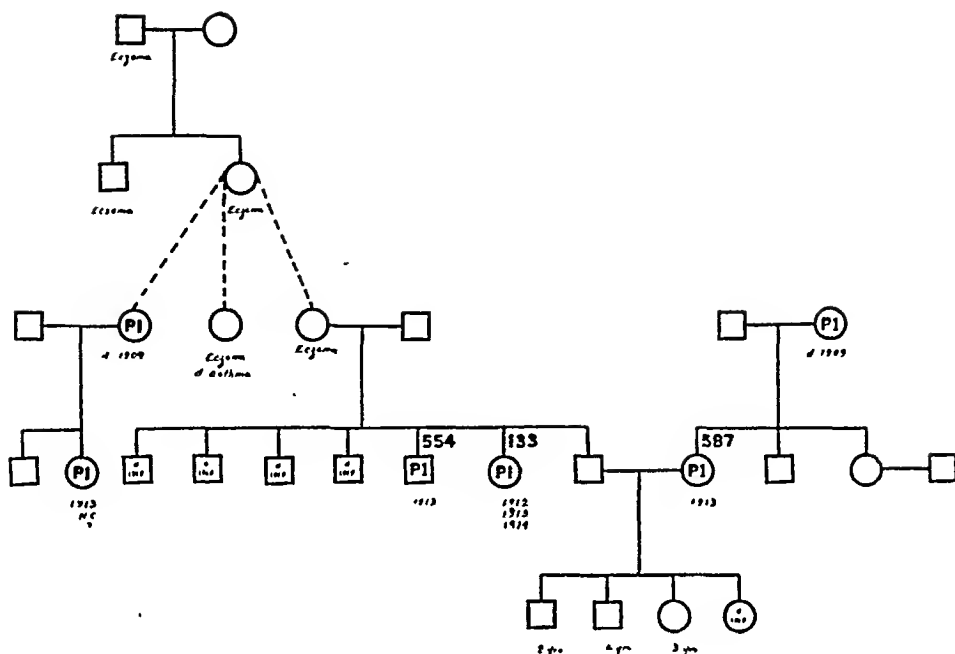


Fig. 25 (C. Family).—The C. family has had eczema as far back as its history can be traced. The maternal grandfather had indigestion and eczema. The mother and uncle both had eczema so badly that the hands had to be wrapped in winter. The mother had three illegitimate children; one, C. B., died in 1904, with all symptoms of pellagra. Her hands and feet were badly broken out and marked gastro-intestinal symptoms and severe mental disturbance occurred before death. Her daughter is said to have developed pellagra in 1913, but as she lives in North Carolina, this report was not verified. One daughter died at the age of 33, with asthma. The other daughter, mother of Pellagrins 133 and 554, has had eczema all her life. The family is living in mill village S in abject poverty. Hygiene, personal and domestic, is unknown. The diet is poor in quality and insufficient in quantity.

In 1910 the family lived in mill village I in a house formerly occupied by a pellagrin. In March, 1912, they moved to S, into a house formerly occupied by Pellagrins 17 and 402. In May, Pellagrin 133, D. C., developed pellagra. She had recurrences in 1913 and 1914. Her brother, Pellagrin 554, W. C., living in the same house, developed pellagra in 1913. He has been in poor health for years. Pellagrin 587, L. C., sister-in-law of Pellagrin 133, visited this house many times, staying night and day. In April, 1913, while here on a visit, she developed pellagra. Erythema was very severe and mental symptoms marked. Three children who accompanied her on the visit have not developed the disease. Her mother, N. S. P., had catarrh of the bowels for years, and in 1909 died with all the symptoms of pellagra. She was cared for by Pellagrin 587.

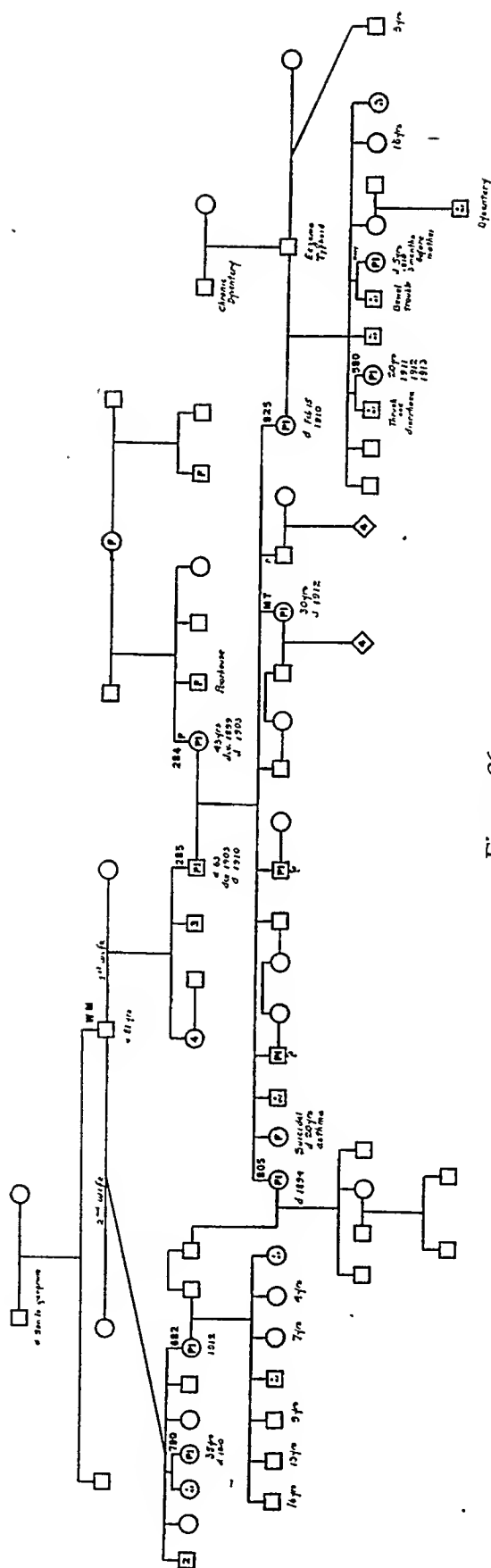


Figure 26.

Fig. 26 (M. Family).—In 1893 Pellagrin 805 went with her husband to the farm of her uncle, where Italian laborers were employed to help with the farmwork. They stayed there during May, June and July, 1893, when they returned home. In the spring of 1894 Pellagrin 805 developed pellagra and died in October of the same year. This was one of the earliest-known cases of pellagra in Spartanburg County. In her fraternity there were ten children. One sister, J. M., was feeble-minded. She had asthma after second year of life. Her mental condition became so marked that she was taken to Columbia Hospital in 1906, where she remained six years. She was suicidal at times. She died at Columbia Hospital in 1912. One brother died at birth. Five brothers are living in various parts of South Carolina and North Carolina. It is reported that two of the brothers are pellagrins, but this has not been verified. One sister, M. T., aged 30 years, died in 1912, of pellagra. Her husband and four children are not affected. One sister, Pellagrin 825, died in 1910 at A. She was very badly affected, and not having any one of the family able to care for her, she was nursed at intervals by various friends and neighbors. She died in 1910. (It is worthy of note that many new cases of pellagra developed in this mill village the following year.) The house was thoroughly fumigated after her death. Her husband has married a second time and has a son aged 3 years. The family are still living in the village. He was the father of ten children by Pellagrin 825.

Two daughters and two sons of this couple are living at home unaffected. One son died at 18 months with thrush and diarrhea. One girl, a twin, died in 1910, three months before her mother, aged 5 years, 7 months. She had erythema, severe bowel trouble, and was "crazy" for six weeks before death. Another baby girl died at birth. One daughter, aged 19, married. She is not affected. Her son died, aged 20 months, of dysentery. She has no other children. Another daughter, Pellagrin 580, who married in 1910, developed pellagra in July, 1911, and has had recurrences in 1912, 1913 and 1914. She had severe mental symptoms in 1913, with stomatitis and bowel trouble. There was a remission during the winter, but early in January there was severe recurrence. She is at present anemic, listless and indifferent to her surroundings. The parental grandmother of Pellagrin 580 had chronic dysentery for years, and her father has eczema, which developed after an attack of typhoid.

The maternal grandmother, Pellagrin 284, a woman of weak intellect, whose mother and two brothers were feeble-minded, developed pellagra in 1899 in A, Spartanburg County, and later moved to S, where she died in June, 1903. Mental symptoms were pronounced for three months before death. The maternal grandfather, Pellagrin 285, developed pellagra at S in 1903. He died at his son's home in Laurens County in 1910. There was complete mental failure before death. He was the only one of seven children known to have pellagra. His father, W. M., lived and died in Laurens County. He was always strong and healthy, and died of old age, 81 years. The brother of W. M. died in the southern part of Spartanburg County, aged 80 years. Their father died of gangrene. W. M. was married twice. His widow is living in E, Spartanburg County. By his second wife there were six children, all living except twin girls. One died in infancy, the other, Pellagrin 790, N. M., died at E, in Spartanburg County in 1910, of pellagra. Her mental symptoms were marked. Another daughter, Pellagrin 692, was reported to have pellagra in 1912. There was no recurrence in 1913 or 1914.

Fig. 27 (T. G. Family).—P. T., the maternal grandfather of Pellagrin 198, died of "chronic bowel trouble." His wife died with heart trouble. Pellagrin 329, N. T., the mother of Pellagrin 198, died of pellagra in October, 1911. She developed it in the early spring. She had the usual skin and intestinal symptoms; her mind soon became affected and she needed constant watching. Her son, Pellagrin 198, spent much time at her house and took care of her at night. Her husband, T. V. G., had died the previous year of typhoid fever. He had chronic bowel trouble for six months, ten years before death, without any recurrence. Pellagrin 329 had serious bowel trouble at the same time, and three years before death, that is, in 1908, she had another attack. T. V. G. had three sisters, whose families are free from pellagra. One brother died in 1895 with typhoid fever. This brother's wife died, aged 66 years, of tuberculosis. They had four children, one of whom, Pellagrin 282, J. C., aged 28 years, developed pellagra in 1910 and had a recurrence in 1911. There has been no known recurrence since, and it was not ascertained whether there was association between the families the year that T. V. C. had typhoid. Pellagrin 282 had five children: three died in infancy before their mother had pellagra, and two, the oldest and the youngest, are living, free from the disease. The youngest was one year old when the mother developed the disease.

Pellagrin 198, T. G., aged 42 years, developed pellagra in 1911, the year his mother died. Erythema appeared on arms, hands and neck. Later, stomatitis and diarrhea occurred. There was a recurrence of symptoms in 1912, but when seen in 1913 and 1914 the patient seemed to have recovered. He has three children, all well; one child died in infancy. One brother of Pellagrin 198 died of heart trouble. One brother, P. G., died of tuberculosis in June, 1914. Six children and his wife are well. Unusual precautions were taken by his wife to prevent infection. One brother, R. G., has had indefinite symptoms of pellagra for four years. He lives near Pellagrin 198, and their families are closely associated. He married a strong woman, but out of five children, only one, a boy 17 months old, is living. One daughter died of cholera infantum, one of whooping-cough, one of meningitis, and one son was born dead. One sister of Pellagrin 198, B. M., Pellagrin 328, developed pellagra in 1911. She had a recurrence in 1912 and in 1913. She has three children, one of whom, M. M., 8 years of age, is macrocephalic. She was "born with bowel trouble" and did not walk for three years. She has never been to school. She is affectionate, but mentally dull and sluggish in movements. F. M., 6 years old, is under-size and has a harelip. G. M., 3 years old, is macrocephalic, and does not walk yet. One sister of Pellagrin 198, L. T., had two illegitimate children. She is now married to an old man and has three other girls. All seem normal.

In April, 1914, Pellagrins 932 and 933, two children of J. G., a second cousin of Pellagrin 198, developed pellagra in mill village P. There has been no association with the other members of the family for years. A family of children living directly across the street from Pellagrins 932 and 933 developed pellagra in 1913 and the children all play together. Two other children, aged 15 years and 13 years respectively, working in the mill, and the baby, aged 3 years, were free from the disease.

(Query: Have these children an inherited weakness, making them more susceptible than a dozen other children who are playmates of these same pellagrins?)

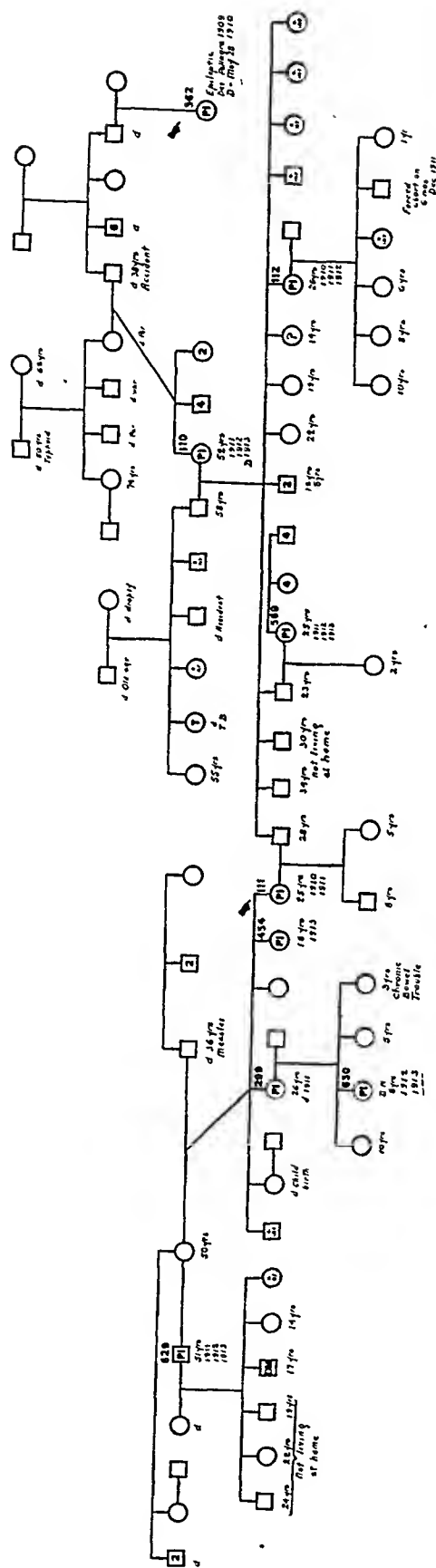


Fig. 28 (H. W. Family).—The members of this family lived in two mill villages where pellagra was endemic. They were poor, ignorant, unclean and degenerate. Conditions in the homes were as bad, if not worse, than in any of the homes visited. This, in spite of the fact that there were several mill workers whose wages, if pooled, would make a larger income than is common in the South.

Pellagrin 110, Mrs. M. H., aged 52 years, visited many of the pellagrins in S mill village and helped to "lay out" several after death. She developed the disease in a very severe form in July, 1911. She had a recurrence in 1912, followed by progressive weakness until her death in 1913. She had four brothers and two sisters, still living and unaffected. Her mother and maternal uncle died of paralysis and her maternal grandfather of typhoid. Her father was accidentally killed when a young man. His family history is very vague, most of his fraternity being dead. He had a niece, Pellagrin 362, A. H., an epileptic, who developed pellagra in December, 1909, in S mill village and died in June, 1910. Nothing definite could be learned of this case except that her symptoms were severe and she was visited by many of the village people. An epidemic of pellagra in S mill village in 1910 and 1911 may or may not have originated here.

Pellagrin 110 married a man who is still living and whose family history is negative to pellagra. One of his brothers was accidentally shot, one died in infancy and one sister died also in infancy; one sister died young of tuberculosis, and one sister is still living and is well. This couple had fourteen children, only one of whom developed pellagra, Pellagrin 112. The wives of two of the sons, Pellagrin 111 and Pellagrin 568, however, developed pellagra. Of the fourteen children, four died in infancy.

Pellagrin 112, Mrs. M. N., aged 26 years, developed pellagra in 1910 and has had recurrences every year since, except in 1914. She lived in the country about a mile from her mother's home. In 1911, owing to persistent vomiting, there was an induced abortion of a 6 months' child. In 1913 a child was born who showed no symptoms of pellagra. There are three older children, aged from 10 to 6 years.

Pellagrin 568, L. H., aged 25 years, married B. H., son of Pellagrin 110. Her father, mother, four sisters and four brothers are living in North Carolina and they have never seen a case of pellagra. She developed the disease in 1911 and had recurrences in 1912 and 1913. A son, born after she developed pellagra, has no symptoms.

Pellagrin 111, Mrs. F. H., aged 25 years, has lived part of the time with Pellagrin 110 and part of the time she has kept house herself. She was a constant visitor at the homes of pellagrins. She developed the disease in 1910. There was a slight recurrence in 1911, but there have been no symptoms since. She has two children, aged 8 years and 5 years, who show no symptoms of pellagra. In her family there are three other cases of pellagra. Her sister, Pellagrin 299, P. D., aged 26 years, living in P mill village, died in 1911 of the disease. She left four children, one a deaf-mute, Pellagrin 630, G. D., aged 6 years, who developed pellagra in 1912, and had a recurrence in 1913. The youngest child has had chronic bowel trouble for three years. No definite history of erythema could be obtained. Pellagrin 454, A. W., aged 18 years, another sister, developed pellagra in 1913. Her stepfather, Pellagrin 629, developed pellagra in 1911. He worked in the mill until this time. He had a recurrence in 1912 and most decided symptoms in 1913, when he was in the hospital for months. He has a deaf-mute son, aged 17 years; also a daughter, aged 14 years, by a former wife. He also has three sons not living with him, none showing any pellagra symptoms.

STUDIES IN CEREBRAL FAT EMBOLISM

WITH REFERENCE TO THE PATHOLOGY OF DELIRIUM AND COMA *

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CHICAGO

INTRODUCTORY

In a previous study¹ of the tissues of fourteen persons who died following fractures complicated by fat embolism, an attempt was made to correlate the amount of fat present in the blood vessels of the various organs, demonstrable by histologic methods, with the severity of the symptoms noted clinically and the frequency with which the delirium occurring after fractures was ascribed to alcoholism was emphasized. In eight of the fourteen, delirium tremens had been diagnosed clinically, although histories of alcoholism had not been definitely established in each of the cases. The study was made on the bodies coming to necropsy from the Cook County and Presbyterian hospitals, Chicago. One of these, which will be called Case A, because of the pronounced clinical manifestations and marked anatomic changes was chosen as the standard.

Preparation of the tissues for purpose of accurate estimation of the fat content was as follows: The tissues were embedded in a 10 per cent. gelatin solution, hardened in formaldehyd vapor at 37 C. for seventy-two hours, or until they were sufficiently hard to permit cutting with the usual sliding microtome, stained with sudan III, and counterstained with hematoxylin, then mounted in glycerol. This method is discussed in the previous report. It has the advantage of keeping the fat globules in their vascular beds, preventing their loss or displacement in cutting, and the counterstain enables a simultaneous histologic study. Sections so embedded were cut to from 5 to 15 microns without loss of the fat globules. Of each piece of tissue, fifty sections were examined; and of these, five sections containing average amounts of fat emboli were set aside for comparison. When these were collected they were carefully examined, and the amount of fat in ten fields of each organ was compared to the amount in ten fields of the same organ of Case A, which was regarded as containing 100 per cent. Then the percentages of fat emboli in the sev-

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1. LeCount and Gauss: A Study of Fat Embolism Associated with Fractures, Tr. Chicago Path. Soc., 1915, ix, 251.

eral organs of each body were averaged and compared to Case A. The result was that the other thirteen bodies were found to contain 5 to 45 per cent. of fat emboli in the organs. The fat emboli were most numerous in the lungs. In addition to the presence of fat emboli, there were certain circulatory alterations, as edema and hemorrhages, besides fatty changes of some of the organs. Edema of the brain was observed in seven, fat droplets in the blood stream noted at the time of necropsy in six, petechial hemorrhages, also noted at the time of necropsy, in the skin or organs in nine. In the lungs of all the bodies there were large numbers of fat emboli, and in half there were microscopic hemorrhages. In the heart muscle of thirteen bodies there were fat emboli, microscopic hemorrhages in twelve and fatty degeneration in six. In the kidneys of all fourteen bodies there were fat emboli, fatty degeneration in thirteen and microscopic hemorrhages in ten. In but six of the livers were emboli found, while in twelve there was venous engorgement and fatty infiltration, the latter being marked in seven. Fat emboli were also found in the brain, suprarenal, gastric mucosa, testis and spleen, in several instances.

Comparing the clinical symptoms of the fourteen patients, one does not find such diversity; on the contrary, the clinical pictures of all have many points in common. All the patients after a variable period of consciousness passed into a restless stage; and in twelve this took the form of delirium, eleven becoming so violent that restraint was applied, and a similar number passing from their delirium into a comatose condition. In all fourteen there was marked dyspnea, and the respiratory rate increased, the maximum rates averaging fifty-three per minute for the fourteen. This average was made from the rates recorded on the history sheets a few hours previous to death. Two of the patients developed Cheyne-Stokes respiration, four suffered from air hunger, and two developed a marked cough. The pulse in all became weak and shallow, the maximum averaging 153 for the fourteen. Urine and feces were passed involuntarily in twelve, and in the other two the records are incomplete. Thirteen of the patients came into the hospital with a normal or slightly subnormal temperature, and in all it rose steadily to the time of death, the maximum temperatures averaging 105.2 for the fourteen. The bones fractured were the femur in four patients, the humerus in three, the tibia and fibula in five, the calcaneus in one and the pelvis in one. The ages of the patients varied from 35 to 90, averaging 53. The time that they lived after injury varied from two to seventeen days, averaging six days. A more complete discussion of this study is given in the previous report, already referred to.

The failure to correlate the amounts of demonstrable fat emboli in the organs with the clinical symptoms was rather to have been

expected, for the amount of fat in the organs varies from time to time. Following a fracture in which fat is liberated from the bone marrow, absorption takes place through the regional veins and lymphatics which are torn by traumatism. The emboli are carried to the venae cavae, thence to the right heart, which pumps them to the lungs, where they become lodged in the capillaries. After a variable period some of the emboli are forced through the capillaries, are returned to the left heart, and are then sent into the general circulation to reach the various tissues, where they again become lodged in the capillaries. Here also they are forced through after a variable period, but are replaced by new emboli which had been temporarily arrested in the pulmonary circulation. The fat is finally excreted, at least in part, by the kidneys.

Observers along other lines of study have frequently noted a failure of correlation between morphologic lesions and functional disturbances. Barker,² who has carefully reviewed the literature on the relations of alteration of the central nervous system following various forms of injury, concludes that the correspondence lies in the finer structural alterations not discoverable by present methods of examination, admitting, however, that histologic alterations have functional equivalents.

In view of the marked cerebral symptoms so often occurring in fat embolism associated with fractures, notably delirium followed by coma, which is so frequently ascribed to alcoholism, a detailed study of the central nervous system was undertaken, with the hope of finding alterations which would establish a pathologic basis for these cerebral symptoms occurring after fractures. This study was suggested by Dr. LeCount, who kindly supplied me the brain of Case A.

LITERATURE

The history of the occurrence of fat emboli in the central nervous system and the resulting symptoms forms the largest and most interesting chapter of the subject of fat embolism. Scriba³ cites Cohn as the first to describe fat emboli in the brain. Cohn in 1860 found them in the capillaries of the cortex, but thought that they were the result of degeneration of the arterial walls. Muller⁴ also in 1860 described fat emboli in the choroid coat of the eye, and he is generally cited by writers as the first to describe fat emboli in human tissue. Bergmann⁵ in 1873 called attention to cerebral fat embolism and suggested its clinical importance. Czerny⁶ in 1875 named it as a possible cause of

2. Barker: *The Nervous System*, New York, D. Appleton & Co., 1901, Chap. 25.

3. Scriba: *Deutsch. Ztschr. f. Chir.*, 1880, xii, 118.

4. Muller: *Wurzb. med. Ztschr.*, 1860, i, 45.

death. Fenger and Salisbury⁷ in 1879 were probably the first in this country to describe fat emboli, as well as multiple ecchymoses in the brain. At this time there were numerous case reports in which cerebral fat emboli or symptoms were mentioned, without contributing new facts. Scriba² in 1880 gives a good description of the brain changes. He found hyperemia, multiple small punctate hemorrhages, anemic areas, fat emboli in the capillaries; and in some of the animals in which he produced experimental oil embolism the brain was edematous and the ventricles dilated. He regarded the changes in the brain and cord as the most important lesions of fat embolism, declaring that death could occur only from changes in the nervous system. Later writers do not agree with this dictum. His account of the clinical symptoms is also complete. He mentions collapse, stupor, disturbances in the pupillary reaction, loss of consciousness, convulsions, coma, etc., and attributes them to changes in the brain. Payr,⁸ 1899, recognized cerebral fat embolism as a distinct clinical form, and divided them into cerebral and pulmonary types. Hamig⁹ in 1900 made a careful study of the clinical aspects of cerebral fat embolism. He reports five cases in which the patients developed the typical symptoms, and in all of whose brains fat emboli were found in the capillaries. He expressed the belief that the clinical symptoms are due to the secondary changes, as hemorrhage and degeneration, rather than the presence of the fat emboli in the vessels. He contends that following many fractures no distressing symptoms of fat embolism occur, although fat may be found in the urine as evidence of the occurrence of fat embolism; and since the brain receives a more direct and larger amount of blood than the kidneys, it must also receive a considerable amount of circulating fat.

As to the time of the appearance of the secondary changes, especially the hemorrhages, there are different opinions. Ribbert¹⁰ says that they appear after the third day following the injury. Grondahl¹¹ found them after fifty hours; Warthin¹² after twelve hours. Ribbert thinks that one third of the deaths associated with fat embolism is due to changes in the brain; Grondahl puts the figure at one half. The latter divides the cerebral symptoms into three stages: the initial stage, before the onset of the symptoms; the second or restless stage, in which the patient frequently develops delirium, and the last or coma-

5. Bergmann: Berl. klin. Wehnschr., 1873, xxxiii, 385.

6. Czerny: Berl. klin. Wehnschr., 1875, xlv, 593.

7. Fenger and Salisbury: Chicago Med. Jour. and Exam., 1879, xxxix, 587.

8. Payr: Ztschr. f. orthop. Chir., 1899, vii, 338.

9. Hamig: Beitr. z. klin. Chir., 1900, xxvii, 333.

10. Ribbert: Cor.-Bl. f. schweiz. Aerzte, 1894, xxiv, 457.

11. Grondahl: Deutsch. Ztschr. f. Chir., 1911, cxi, 56.

12. Warthin: Internat. Clin., 1913, iv, Series 23.

tose stage. Amberg¹³ lays great stress on the recognition of the initial stage as an early diagnostic point of fat embolism. As pointed out by Benestadt,¹⁴ the changes in the brain are not necessarily fatal. He reports the cases of three patients who developed symptoms of fat embolism following fractures of bones. All three passed through the first two stages and subsequently recovered. Godlee and Williams¹⁵ contribute a valuable article on cerebral fat embolism in which the association of the cerebral symptoms and brain changes seem to be quite evident. In a railroad accident there were nineteen persons who sustained fracture of one or more bones. Of these, four died, one almost immediately, and the other three after different periods following the accident. In one of the last three a postmortem was not allowed, but in view of the almost identical symptoms, they think that he also possessed the same anatomic changes. One patient suffered from a simple fracture of the femur. He was brought to the hospital within one hour and had not lost consciousness, but that evening he became comatose and could not be roused. His pulse was 130, temperature 103, and respiration was of the Cheyne-Stokes type. He remained in coma and died four days later. Another patient suffered from a crushing injury of both femurs. He also was fully conscious when brought to the hospital, but within a few hours he became restless, his pulse was 160, temperature 102, and rapid respiration of the Cheyne-Stokes type. The following morning he became comatose and died on the second day. The brains of these two patients contained many punctate hemorrhages, and on microscopic examination the capillaries were found filled with fat emboli, and there were numerous small hemorrhages.

In our series all the patients developed marked cerebral symptoms. Five were brought to the hospital in the restless stage, and one was wildly delirious. In the case of these five a period of several hours had elapsed after the injury. The others suffered from no distressing symptoms on admission, but became restless in twelve to twenty-four hours. Most of them lay for hours at a time muttering incoherently, tossing about their beds and trying to get up. They became stuporous in twelve to thirty-six hours, and gradually comatose in twenty-four to seventy-two hours, from which they could be aroused at first by supra-orbital pressure, but later failed to respond. One patient partly recovered from his symptoms, but had a relapse, and two remained delirious for about ten days. In two patients the pupils were constricted on admittance, but dilated before death; one developed ptosis of one lid subsequent to his admittance and one strabismus.

13. Amberg: *Wien. klin. Rundschau*, 1914, xxviii, 95.

14. Benestadt: *Deutsch. Ztschr. f. Chir.*, 1911, cxii, 194.

15. Godlee and Williams: *Lancet*, London, 1911, i, 1062.

EXPERIMENTAL DEMONSTRATION OF THE INFLUENCE OF FAT ON
THE CIRCULATION

In order to obtain some idea of the processes that take place in the capillaries following the entrance of fat emboli, the following experiments were devised to study the viscosity of the blood in fat embolism, also the capillary resistance associated with the altered conditions of the blood. It is realized that these capillary experiments cannot be held a strict counterpart of the phenomena that take place in the blood vessels, in view of the ability of the blood capillaries to alter their physiologic state in response to altered physical states of the blood; nevertheless, for a given instant, the conditions may be regarded as being analogous. The experiments were repeated a sufficient number of times to insure uniformity of results.

To determine the alterations in the viscosity of the blood, a simple apparatus was set up for measuring the rate of flow of fluids through a long capillary tube of a small bore, under constant pressure. The apparatus consists of a capillary tube 30 cm. long having a bore of less than 1 mm. connected with a 5 c.c. glass bulb used as a reservoir for the fluids to be tested, which in turn is connected with a buret containing a column of water having a pressure of 70 mm. mercury. A T tube placed between the bulb and the buret is used to empty and refill the bulb (Fig. 15). One cc. of the fluid was allowed to flow through the capillary, the amount being determined on the buret. A series of fluids was then examined, for the rate of time that it required 1 c.c. to flow through the capillary; in each instance the experiment was started with the column of water in the buret having a pressure equal to 70 mm. mercury. Emulsions were then made, using 9 c.c. of each of the respective fluids and 1 c.c. olive oil, and the rate of flow determined. To insure the proper escape of the emulsions through the capillary, the bulb was placed slightly lower than the capillary; and to eliminate the source of error due to alterations of the emulsions by mixture in the T tube, only the first cubic centimeter was measured, the remainder being discarded. The following results were obtained:

TABLE 1.—TIME REQUIRED FOR ONE CUBIC CENTIMETER OF FLUID TO PASS
THROUGH THE CAPILLARY UNDER CONSTANT PRESSURE OF 70 MM. HG.
AND CONSTANT TEMPERATURE OF 24.5 C.

	Alone, Seconds	Plus Olive Oil, Seconds
Salt solution	33	100
Ascitic fluid	45	130
Human blood serum.....	57	180
Human blood slightly diluted with citrate solution.	160	480

As seen from the table, the viscosity of the blood is increased approximately four times in these experiments, which gives ground for the belief that a similar increase may occur in fat embolism. In study-

ing the resistance occurring in capillary tubes the same apparatus was used, the resistance being measured in terms of millimeters of water as determined by the height of the column in the buret required to force the fluid through the capillary. The system was filled with water until the water level in the buret was the same as in the capillary. In this condition no fluid escaped from the open end of the capillary. The column of water was then raised until the fluid just escaped from the capillary. The column of water above the capillary being read in millimeters was taken as the pressure necessary to overcome the capillary resistance. The same series of fluids was tested. The figures in the first column of the following table give the pressure required to cause the several fluids to pass through a capillary 205 mm. long and one-fourth mm. in diameter. In the second column is given the pressure required after the addition of olive oil, mixed as in the previous experiment. It is seen that it required approximately ten times the pressure after the addition of the oil. Various sized capillaries ranging from 10 microns to 1 mm. in diameter were used, and the same principle was observed in all. The figures, however, denote only approximate relationships, for one of the variable factors was the size of the oil droplets, and this factor we were able to control only approximately. The principle, however, of increased capillary resistance of fluids following the addition of oil nevertheless holds true.

TABLE 2.—PRESSURE IN MILLIMETERS OF WATER REQUIRED TO OVERCOME THE CAPILLARY RESISTANCE OF A TUBE 205 MM. LONG AND ONE-FOURTH MM. IN DIAMETER; TEMPERATURE 23 C.

	Alone, mm.	Plus Olive Oil, mm.
Salt solution	4	41
Ascitic fluid	5	46
Human blood serum.....	5	49
Human blood slightly diluted with citrate solution..	11	95

These tables at least give an idea of the processes taking place in the capillaries, and help explain the obstruction to the circulation which results in the observed phenomena of focal edema, focal hemorrhages and focal necrosis following the entrance of fat into the blood vessels.

REPORT OF CASE *

The clinical history and pathologic alterations of the subject of this study are as follows: Patient A, a railroad fireman, 35 years old, was struck on the head by a projection of a low viaduct while removing the signal flags from the top of the tender, Oct. 4, 1909. He was picked up unconscious by the engineer, who said that the patient's leg was doubled under him. He was

* As noted in the previous report (LeCount and Gauss, loc. cit.) Dr. Evarts A. Graham reported some of the details of this case of fat embolism to the Illinois State Medical Society March 23, 1910, but so far as known did not have them published.

brought to the Presbyterian Hospital, several hours later, and by this time had recovered consciousness. There was found on examination a superficial scalp wound over the left anterior parietal region, although no skull fracture could be determined, a fracture of the tibia at the junction of the middle and lower thirds, and a fracture of the fibula above that of the tibia. A diagnosis of the fracture of the tibia and that of the fibula of the left leg was made, to which was added later, complication by fat embolism.

The patient lived four days. On admittance he was fully conscious and answered all questions, though somewhat slowly. His pupils were equal and exhibited no abnormal signs. The muscular power was equal in both hands, there was good movement of the toes, the general cutaneous sensations were equal on both sides, the tongue was extended in the median line when the patient was asked to do so, and he did not complain of headache or dizziness. He remained quiet all day, but toward evening complained of pain. He took nourishment when fed, and appeared dull mentally. He slept nearly all of the night. On October 5 he awoke at 8 a. m., and complained of pain in the back. He became restless and morphin was administered, but the restlessness continued during the morning and afternoon. In the late afternoon he became drowsy, then stuporous and failed to respond to questions. He was temporarily aroused by supra-orbital pressure. He ate little. On October 6 he was in coma; the pupils had contracted to pinpoint size, the eyes were turned upward, and there was a slight strabismus with deviation to the left. Later in the day the pupils enlarged, and the patient sank deeper into coma, from which he could not be aroused to consciousness, by supra-orbital pressure. He continued in this state to the time of his death, October 7, at 3 p. m. The respiration on admittance was normal in rate and rhythm. On the morning of October 5 it became irregular; by the afternoon it developed into the Cheyne-Stokes type, in which form it continued. On October 7 the patient developed singultus, the breathing became labored, and there was dulness and bronchial breathing over the right lower lobe posteriorly and many coarse râles were heard. The respiratory rate, which had been steadily increasing, reached 64 per minute before his death.

The pulse was normal on admittance, with a rate of 74. It increased steadily, reaching 164 per minute before his death. On October 6 the patient became cyanotic, this condition becoming more marked the next day. Blood drawn from the patient contained fat droplets. The patient perspired profusely during the last few days. Urine and feces were passed involuntarily. Petechial hemorrhages were first noticed at 8 a. m. on October 5, in the scapular regions. They developed rapidly, breaking out in crops. On the morning of October 6 they were all over the trunk, and by noon the neck was also covered with them. The temperature on admittance was 97.8. It rose steadily during the four days, reaching 106.2 before his death.

The postmortem examination was performed the following morning by Dr. E. R. LeCount. Anatomic diagnosis: "Comminuted fracture of the tibia; fracture of the fibula and skull; petechial hemorrhages of the skin, conjunctiva, serous and mucous membranes; parenchymatous hemorrhages of the lungs; hemorrhages in the anterior mediastinum; infarction of both testicles, with fatty changes; icterus; cloudy swelling of the kidneys; recent operative wound of the head; therapeutic puncture wounds of the trunk (sodium chlorid infusion); latent tuberculosis of the lungs; fibrous pleuritis and peritonitis; fibrous mural endocarditis; edema of brain."

From the necropsy record the following items are taken: "Over the trunk, especially the upper part, were innumerable minute petechial hemorrhages, which were in some places clustered, but over the upper part of the chest they were 1 cm. apart. In the pericardium were numerous petechial hemorrhages, which varied in size, some being 1 cm. long and irregular. The lining of the right heart chamber contained numerous small hemorrhages. Both of

the testicles were studded with minute hemorrhages. In the roof of the left orbit there was a fracture, obliquely directed, 2.5 cm. long, with the forward end out. There were small hemorrhages in the gastric mucosa."

In microscopic preparations fat emboli were found in the brain, lungs, myocardium, kidneys, suprarenals, liver and testis. All sections of the lung contained emboli in large amounts. They were well distributed in the capillaries throughout the lung. In shape the emboli were round, oval or elongated; in size from 10 to 50 microns. Under high power there were observed many capillaries running across the microscopic field filled and distended with strings of emboli. The arteries and capillaries were engorged. There were scattered areas of lung tissue in which the alveolar spaces were filled with a hemorrhagic exudate. All sections of the kidney contained emboli, found chiefly in the capillaries of the glomeruli. Nearly all the glomeruli contained some emboli, and about one third were completely blocked by them. In shape the emboli were irregular and tortuous, lying in and distending the glomerular capillaries. Many of the vasa afferentia contained elongated emboli at the entrance to the glomerulus, some 50 to 80 microns in length. The capillaries and arteries were engorged, and there were small intertubular extravasations of blood.

The liver contained emboli in small amounts, found in the capillaries between the hepatic cords. In some of the sections there were capillaries measuring about 100 by 30 microns, which were filled with strings of emboli from 20 to 30 microns in diameter. Near the central veins of many of the lobules the hepatic cells had undergone fatty degeneration. Many of the capillaries just beneath the hepatic capsule contained emboli. There was venous and capillary congestion. All sections of the heart contained emboli, chiefly in the capillaries between the muscle cells. They were round, oval, elongated or spindle-shaped and from 10 to 40 microns in diameter. The muscle cells adjacent and near the emboli had undergone fatty degeneration. These areas of fatty degenerated tissue, containing emboli, were separated from each other by normal tissue in which there were few or no emboli. There was also considerable infiltration of the myocardium by fatty areolar tissue. The arteries and capillaries were distended with blood.

Most sections of the suprarenal contained emboli in the capillary sinuses between the cells of the zona fasciculata, also in the zona glomerulosa. The emboli were elongated and from 20 to 40 microns. In the zona fasciculata there were distended straight capillaries running across the high power microscopic field filled with emboli of various sizes and shapes. The parenchyma cells contained more than the usual amount of fat, especially in the zona fasciculata. A few sections of the testis contained emboli in the capillaries about the seminiferous tubules, from 10 to 20 microns, and usually elongated. The interstitial tissue contained numerous fine fat droplets, suggesting fatty degeneration. The seminiferous tubules were normal.

Study of Brain.—The brain was placed in 10 per cent. dilution of liquor formaldehydi for preservation, and in this condition it was received for study. The brain was normal in size, weight and configuration. The gyri were of normal width and the sulci of normal depth. The pial vessels were moderately engorged. The arteries at the base of the brain were collapsed and there were small regions of thickening in the basilar, posterior cerebral, and middle cerebral arteries. On surfaces made by sectioning the brain transversely there were several small hemorrhages in the anterior half of the corpus callosum, especially in the genu. These hemorrhages measure from 0.5 to 2 mm. in diameter. They were well defined, sharply limited and generally were round or slightly irregular. Similar punctate hemorrhages were found in the white substance throughout the entire cerebrum, especially in the frontal and parietal lobes. The lateral ventricles were moderately dilated.

A preliminary examination of sections taken from the frontal, parietal and occipital lobes was made, and there were found in all the sections fat emboli,

hemorrhages, and foci of degeneration. A more detailed study of this brain was undertaken to (a) identify these alterations with relation to the intrinsic circulation of the encephalon, (b) to study the finer histologic alteration in the areas of focal degeneration by means of differential stains, and (c) to localize the lesions with reference to the various functional centers and pathways of the brain.

It became evident that an accurate identification of the various sulci and gyri of the brain was essential. This was done with the aid of numerous standard textbooks on the morphology of the brain, which were freely con-

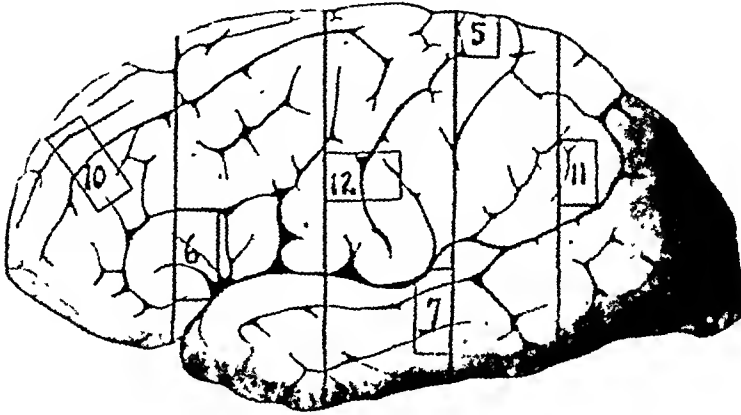


Fig. 1.—Plot of brain, giving lateral view of convex surface of the left cerebral hemisphere, and showing configuration and the location of the sections removed for study; reduced.

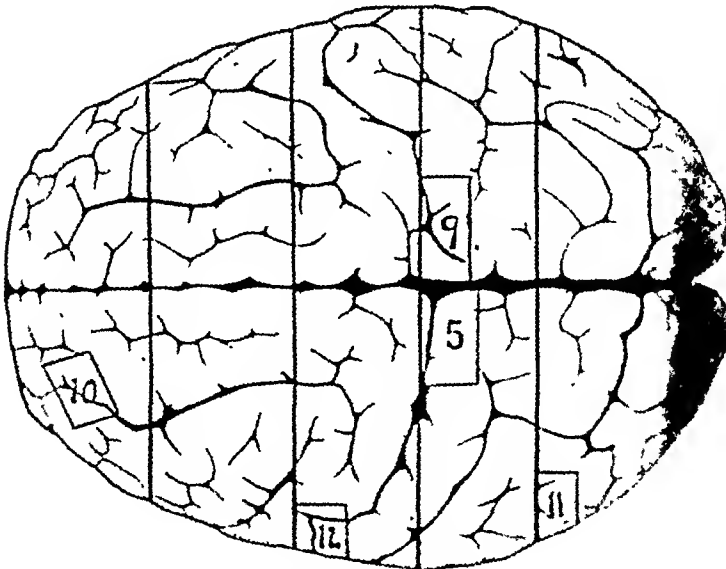


Fig. 2.—Plot of brain, representing convex surface from above, and showing configuration and the location of sections removed for study; reduced.

sulted. The brain was then accurately plotted. Four views were made; a lateral view of the left hemisphere (Fig. 1), a view of both hemispheres from above (Fig. 2), a view of a transverse section just anterior to the mammillary bodies (Fig. 3), and a mesial view of the left hemisphere (Fig. 4). These plots were made as follows: A plane resting on a prominent point of the cortex was imagined, all points of the sulci projected to it by parallel lines, measured with a ruler and drawn; that is, it is as if a piece of glass were laid on the brain, which being held firmly in the desired position, its configuration was copied with a wax pencil, the range of vision being kept constant.

It would of course have been desirable to examine all of the functional areas of the brain; however, such a study was beyond the scope of our present effort, and consequently only representative areas were examined, these being chosen from the more important known centers. They were taken from the following regions as indicated in Figures 1, 2, 3 and 4:

1. Spinal cord at the upper border of the decussation of the pyramidal tract.
2. Vermis cerebelli.
3. Right cerebellar cortex and dentate nucleus.
4. Left cerebellar cortex and dentate nucleus.
5. Left cerebral cortex, central sulcus, leg area, sensory and motor sides.

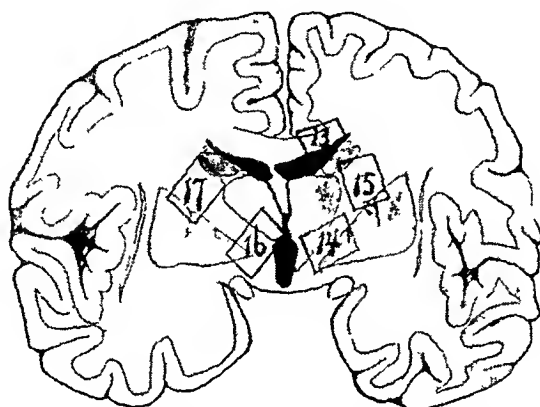


Fig. 3.—Plot of brain, representing transverse section just anterior to the mammillary bodies, and showing the location of the sections removed for study in relation to the internal capsule and the internal nuclei; reduced.

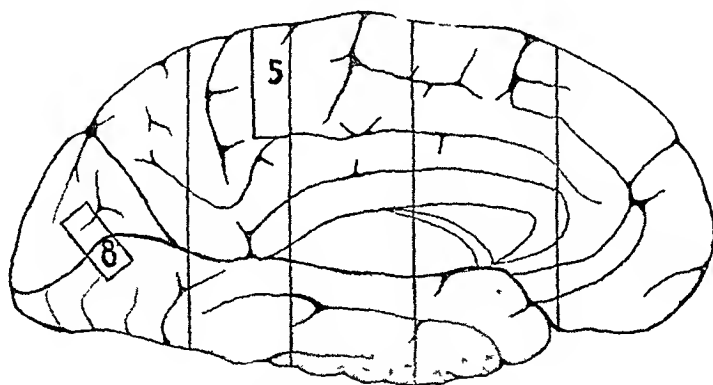


Fig. 4.—Plot of brain, representing mesial surface of left cerebral hemisphere, and showing configuration and location of sections removed for study; reduced.

6. Left cerebral cortex, triangular part of inferior frontal gyrus, motor speech area (Broca's convolution).
7. Left cerebral cortex, superior and middle temporal gyri, auditory area.
8. Left cerebral cortex, calcarine fissure, including portions of the cuneus and lingual gyri, vision area.
9. Right cerebral cortex, leg area, central sulcus, including sensory and motor sides.
10. Left cerebral cortex, superior and middle frontal gyri, association area.
11. Left cerebral cortex, gyrus angularis, inferior parietal lobule, association area.

12. Left cerebral cortex, central sulcus, arm area, including sensory and motor sides.

13. Body of corpus callosum near the middle of its anteroposterior extent, right side.

14. Right ventral limb, internal capsule, including portions of the globus pallidus and thalamus. This and the following three sections were taken from a transverse section of the brain just anterior to the mammillary bodies.

15. Right dorsal limb, internal capsule, including portions of the putamen and caudate nucleus.

16. Left ventral limb, internal capsule, including portions of the globus pallidus and thalamus.

17. Left dorsal limb, internal capsule, including portions of the putamen and caudate nucleus.

Large blocks of tissue several centimeters in length were removed from these areas, and these in turn were cut into smaller blocks and rehardened, frozen and cut, or embedded in paraffin or gelatin, according to the need. In order to bring out as many of the neurologic elements as possible, as well as the pathologic lesions, a variety of stains were used, including sudan III, osmic acid, hematoxylin and eosin, Mann's methylene-blue eosin, toluidin-blue Nissl stain, phosphotungstic acid hematoxylin, Marchi, Golgi, Weigert's myelin sheath stain, Weigert's neuroglia stain, the Ranson-Cajal neurofibril stain, Bielschowsky neurofibril stain, Heidenhain iron hematoxylin stain, Apathy after-gilding chlorid stain. These stains were adapted to the material examined. In view of certain postmortem alterations which occurred in the central nervous system, sections of another brain obtained about the same time and preserved in a similar manner were run in a parallel series as a control, to eliminate artifacts of preparation and postmortem changes.

The alterations will be discussed under the several headings of edema, hemorrhages, fat emboli, focal necrosis, changes in the nerve cells, round cell infiltration, changes in the spinal tracts.

Edema: This condition was observed in the fresh brain at the time of the postmortem. At the present examination after formaldehyd fixation, the ventricles are moderately dilated. It is of course impossible to make any observation of the intermeningeal fluid content. Microscopically, many of the ganglionic cells of the dentate nucleus and of the pyramidal layer of the cerebral cortex are slightly swollen; in the Purkinje layer of the cerebellum there also occur groups of cells that appear swollen. In the cerebral cortex there are present small diffuse areas that suggest focal edema. These areas are associated with fat emboli, and are found principally in the portion included by the lamina granularis interna and the lamina multiformis, and in the molecular layer of the cerebellum. These focal areas are irregular in shape and cover an area whose greatest diameter varies from 500 to 900 microns. Observed in sections stained with Mann's methyl-blue eosin,¹⁶ there are seen scattered through these areas empty capillaries, markedly distended, round or oval in outline, which represent the site of fat emboli. About these vessels are irregular shaped small clear spaces that are extravascular. The extravascular spaces are much more numerous than the larger, definite intravascular spaces, and they comprise the bulk of the focus. The neurophil in these foci appears slightly compressed.

Hemorrhage: Grossly punctate hemorrhages are easily seen in the anterior genu of the corpus callosum and in the white substance beneath the cortex of the cerebrum (Figs. 5 and 6). Microscopically, small hemorrhages are found in all the blocks removed for study. Of each block of tissue removed for study, from

16. Encyklopädie der Mikroskopischen Technik, Berlin, 1933, i, 242.

fifty to two hundred sections were examined, and in about half of these hemorrhages are present. The distribution is uniform in all the blocks when compared to each other. In the spinal cord they occur principally in the gray matter. In one run of sections, the posterior horn, the gelatinous substance of Rolando is a common site (Fig. 7). In the cerebellum a count of one hundred hemorrhages was made. There are forty-four in the granular layer, thirty-two about the Purkinje cells, twenty-one in the molecular layer, two in the dentate nucleus, and one in the medullary substance. In a count of one hundred in the cerebral cortex, the three blocks removed from the central sulcus being used, the distribution is as follows: one in the lamina zonalis, four in the lamina granularis externa, fourteen in the lamina pyramidalis, three in the lamina granularis interna, seventeen in the lamina ganglionaris, twenty-four in the lamina multiformis and thirty-seven in the medullary substance. In the corpus callosum, internal capsule and portions of the adjacent caudate, thalamus and lentiform nuclei, the hemorrhages are present in large numbers (Fig. 8). The hemorrhages cover an area whose largest diameter varies from 100 to 700 microns, generally 300 to 500. They are sharply defined, round or oval in outline, commonly placed about a capillary, the lumen of which is distended, appears empty in the paraffin sections, but is frequently seen to contain a single fat embolus in the gelatin-embedded and fat-stained sections. The hemorrhages are compact, but occasionally appear as circular bands (Fig. 9).

Fat Emboli: These are present in every section stained with sudan III or osmic acid, after gelatin embedding or frozen section. In the spinal cord they are present in both the white and gray substance, more frequently in the latter. In the cerebellum the order of frequency is as follows: molecular layer, Purkinje layer, dentate nucleus, granular layer, and medullary substance. In the cerebrum they are present in largest numbers in the middle layers of the cortex included in and between the lamina pyramidalis and lamina ganglionaris. The peripheral layers and medulla contain lesser amounts. The number of fat emboli per low power microscopic field varies from ten to fifty, they are long, cylindrical, club shaped, or occur in strings of small, round globules, and some of the longer emboli measure 100 microns in length. Many occlude the vessel in which they lie, and branch with it at a point of bifurcation (Fig. 10). In some of the microscopic fields measuring 250 microns under high power, there are capillaries running across the field that are filled with emboli.

Focal Necrosis: In addition to the areas described under "focal edema," characterized by a diffuse area containing many small clear spaces surrounding the sites of multiple fat emboli, there are present smaller, sharply defined areas which will be described under the term "focal necrosis." The appearance of these areas varies somewhat with the stain employed. They are, however, observed with most of the stains used. Within their border there seems to be a loss of some of the neurologic elements, so that they appear as light staining areas surrounded by the normal darker staining tissue. These areas are round, oval or spindle shaped, and frequently placed about a single capillary occluded by fat emboli. In the methyl blue eosin preparations there appears to be a loss of the eosin staining elements. The loss is most marked toward the periphery of the focus where it terminates abruptly at the border; towards the center of the lesion the loss is less marked. In some of these there is an increase of the neuroglia cells in the centers. In other foci the loss of tissue is uniform, the center and periphery staining alike. A few foci with clear centers are surrounded by hemorrhagic bands, suggesting the hemorrhagic infarct. In the phosphotungstic acid hematoxylin preparation there is a loss of the blue staining elements, with an apparent decrease of the neuropil or *Punksubstanz*, the fine granular background of the tissue. In Weigert myelin sheath stained preparations definite information is obtained of these foci. Here is seen a loss of the



Fig. 5.—Photograph of transverse section of brain just anterior to the mammillary bodies. In the corpus callosum there are punctate hemorrhages.



Fig. 6.—Photograph of transverse section of brain just anterior to the poles of the temporal lobes. In the corpus callosum and frontal lobes there are punctate hemorrhages.

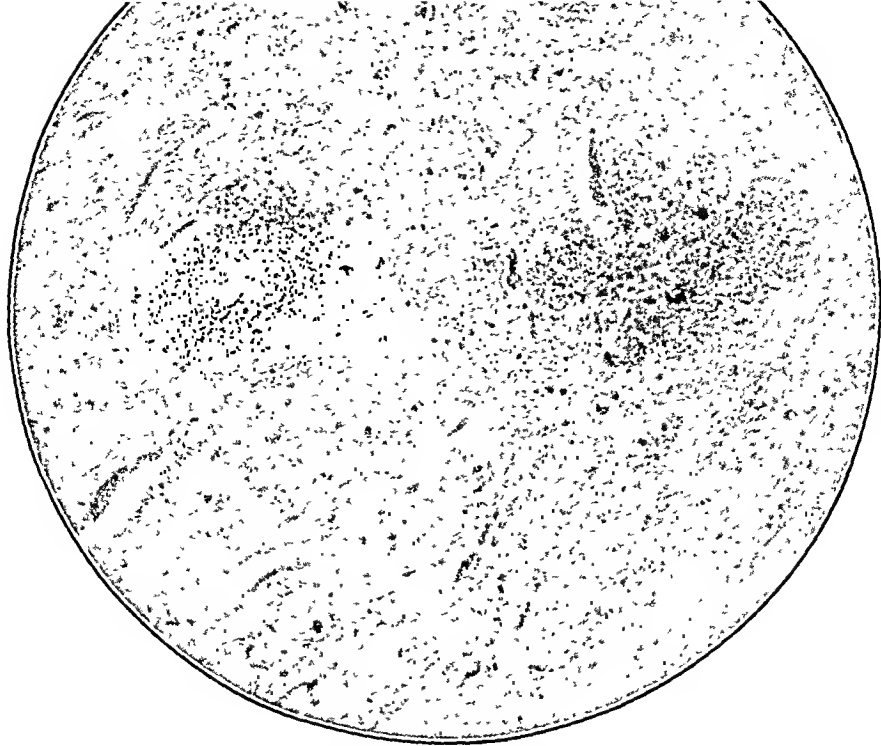


Fig. 7.—Photomicrograph, $\times 110$, showing hemorrhage and round cell infiltration into the gelatinous substance of Rolando, dorsal gray horn of spinal cord at level of decussatio pyramidum; methyl blue eosin stain.



Fig. 8.—Photomicrograph, $\times 60$, showing hemorrhage and round cell infiltration into the ventral limb of the left internal capsule; at left of the photomicrograph is an adjacent portion of the thalamic nucleus, taken from a transverse section of the brain just anterior to the mammillary bodies; methyl blue eosin stain. Block 16.

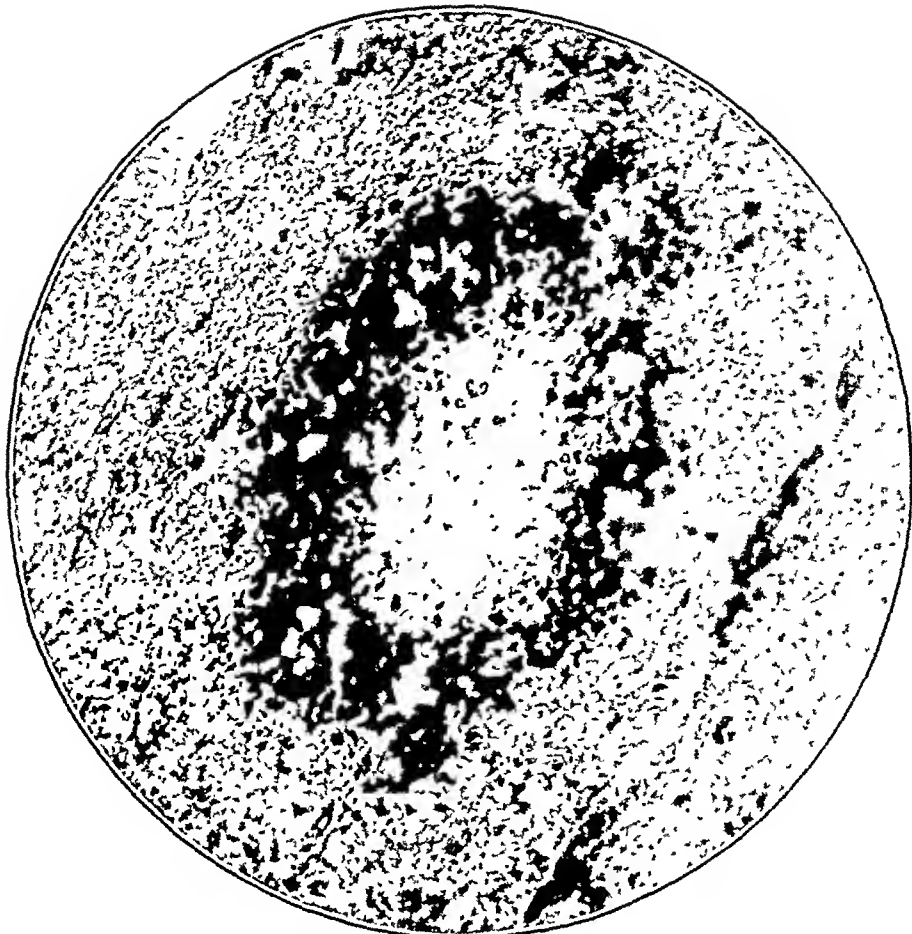


Fig. 9.—Photomicrograph, $\times 230$, showing circular hemorrhage in the leg area of the precentral gyrus, right hemisphere; Weigert myelin sheath stain. Within the hemorrhage the myelin sheaths are entirely destroyed.

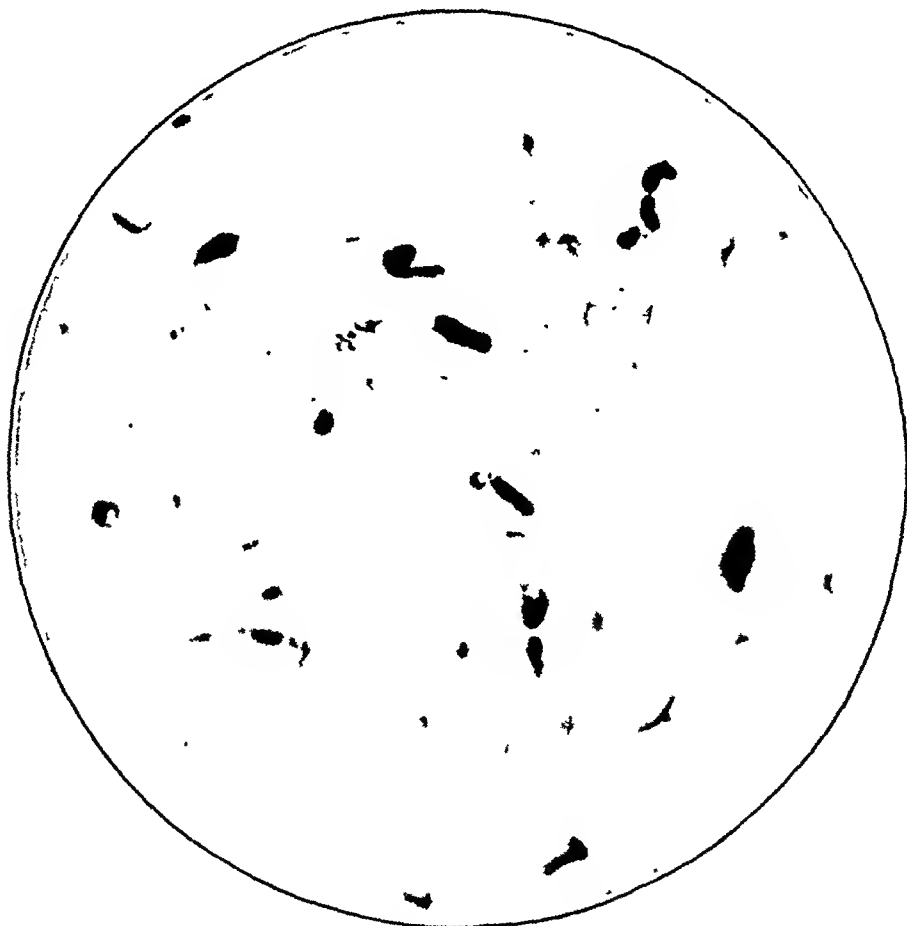


Fig. 10.—Photomicrograph, $\times 110$, showing fat emboli in cerebellar cortex;

myelin sheath (Fig. 11). In some of the foci, there is a total loss of the myelin sheath, but in general a few sheaths are present, these being thinner and more granular than the sheaths of the surrounding tissue, although occasional strands of sheaths traverse the focus and appear to be unaltered. In a few foci seen in the leg area of the left central sulcus a peculiar type of lesion is present. It is a circular hemorrhage, within which there is a total loss of myelinated fibers (Fig. 9). In the silver-pyridin preparation for neurofibrils further information is obtained of these foci. Here is seen a loss of neurofibrils. In the lesions found in the medullary substance of both cerebrum and cerebellum this means a localized destruction of the axones. In some of these foci nearly all of the neurofibrils are lost, in others varying amounts up to about one fourth remain¹⁷ (Fig. 12).

Within the focus the remaining neurofibrils are more irregular and broken up than in the surrounding tissue, although here also a few unaltered strands are present. These foci are present in every block of tissue removed for study and in the majority of the sections. As many as six to the low power field are observed. All parts of the brain are equally affected, there being no noticeable difference in the sections from the various areas of the cerebrum or cerebellum. Within each section they seem to predominate in the regions of the myelinated axons. In one hundred counted in the cerebellum there are forty-three foci in the dentate nucleus, thirty-eight in the medullary substance, fourteen in the granular layer, and five about the Purkinje cells. In the cerebrum, one hundred foci being counted, all are in the medullary substance or in the cortex immediately adjacent to it.

Nerve Cell Changes: The loss of myelin sheaths and axons demonstrable in the preparations just discussed permits an interpretation of the changes in the nerve cells with a greater degree of certainty. The dentate nucleus is a very common site of the focal necrosis. Many of the ganglionic cells in the region of these foci, including those cells within the focus, immediately adjacent to it or a short distance from it, appear to have undergone profound changes. The Weigert preparation, in which destaining had been arrested before the cell bodies were fully decolorized, was chosen for this study because in it are seen the cell changes in relation to the focal necrosis of the myelin sheaths. A normal cell in this preparation is polygonal in shape and has a definite outline, although no definite cell membrane is visible; there are several dendritic processes attached to it for a short distance. The cytoplasm is finely granular and stains deeply, the nucleus is centrally placed, generally round in shape, occupies about two fifths of the diameter of the cell, contains a dark intensely staining nucleolus centrally or slightly eccentrically placed, which is surrounded by a clear zone containing some light staining chromatin. In the early changes observed in these cells there is a shifting of the nucleus so that it occupies an extremely eccentric position, coincident with the cell assuming a round or oval appearance in place of the more polygonal form; the cytoplasm may still stain deeply. In other cells the nucleus has remained central, but the nucleolus occupies an extremely eccen-

17. Our material had been in formaldehyd for several years. Several neurofibril stains were tried with unsatisfactory results. A definite, clear-cut picture of the axons and dendrites that would permit of quantitative as well as of qualitative study was not obtained, either through faulty technic or acid reduction of the neurofibrils by the commercial formaldehyd used as the preservative. After numerous trials, it was found that if small pieces of tissue 1 cm. square and not over 2 mm. thick were placed in a 1 per cent. ammonia solution for twenty-four hours with repeated changes, then placed in a 1 per cent. ammoniacal 95 per cent. alcohol for seventy-two hours, with repeated changes, then fixed according to the method given by Ranson (*Jour. Comp. Neur.*, 1912, xxii, 487) starting with 1 per cent. ammoniacal absolute alcohol and increasing the period of silver impregnation to from four to five days, a very satisfactory neurofibril preparation resulted from the formaldehyd fixed material.

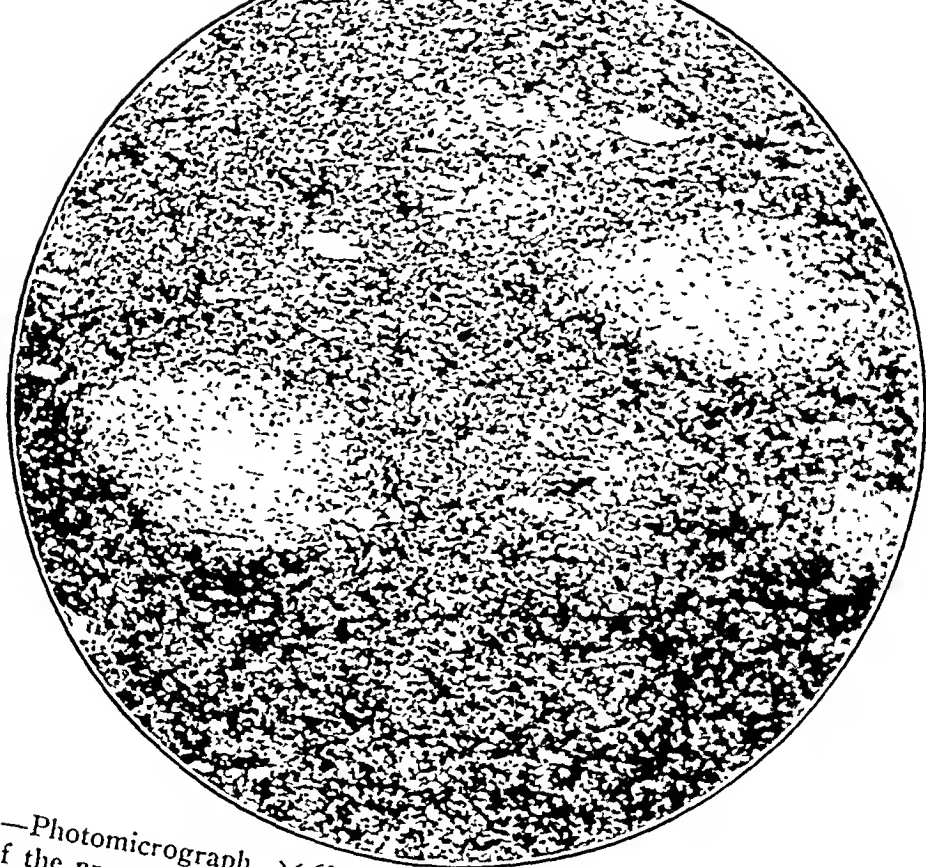


Fig. 11.—Photomicrograph, $\times 60$, showing multiple foci of necrosis in the arm area of the precentral gyrus, left hemisphere; Weigert myelin sheath stain. In the light staining areas there is a loss of most of the myelin sheaths.

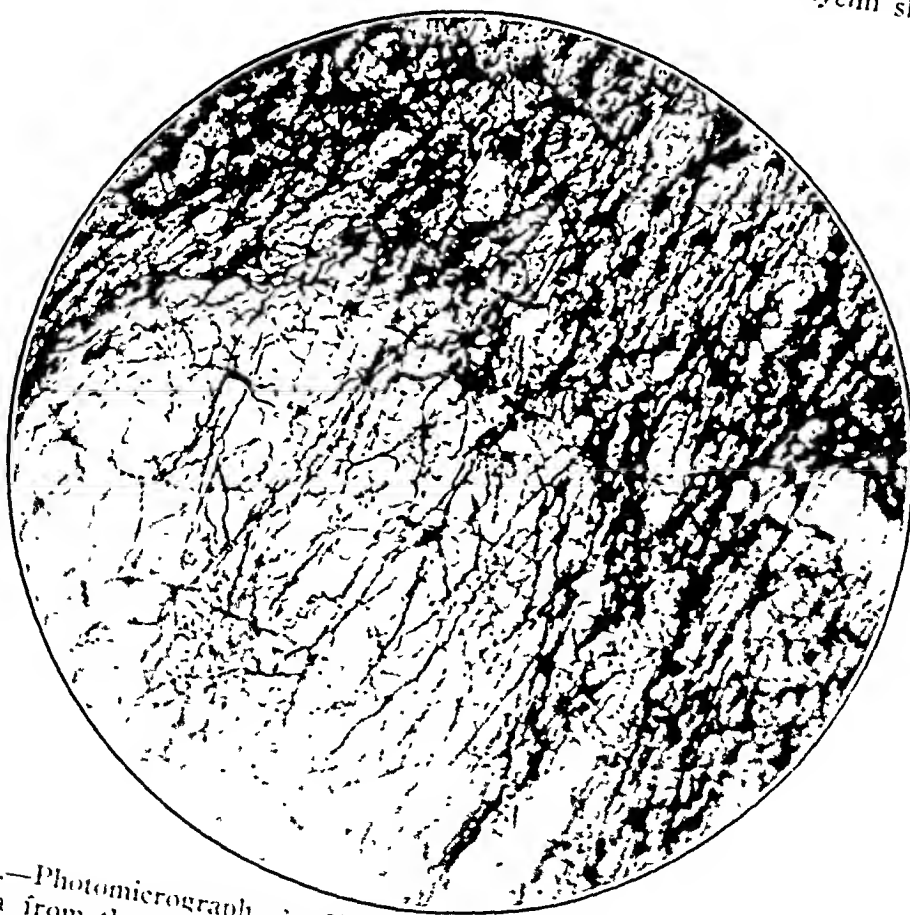


Fig. 12.—Photomicrograph, $\times 325$, showing focal necrosis in the motor speech area from the triangular part of the inferior frontal gyrus of the left hemisphere. Silver pyridin preparation for neurofibrils. Within the focus four fifths of the axons have been destroyed.

tric position. The cells that have undergone further changes look swollen with the entire pattern slightly blurred. The cytoplasm stains lightly, the nuclear membrane is irregular, broader and less distinct; the nucleus appears swollen and may occupy one third to one half of the diameter of the cell; the nucleolus is also swollen and less distinct; and there is an increase in the stainable nuclear chromatin. In still later changes the nucleus has entirely disappeared and all that remains of the cell is a round or club shaped mass of granular, irregular staining protoplasm, containing a lighter staining round area placed near its center or eccentrically (Fig. 13). These changes are observed in many of the cells of the dentate nucleus and to a lesser extent in the pyramidal cells of the cerebrum. Whether they are consequent on the changes in the axons and myelin sheaths cannot be determined on the basis of this single study; although

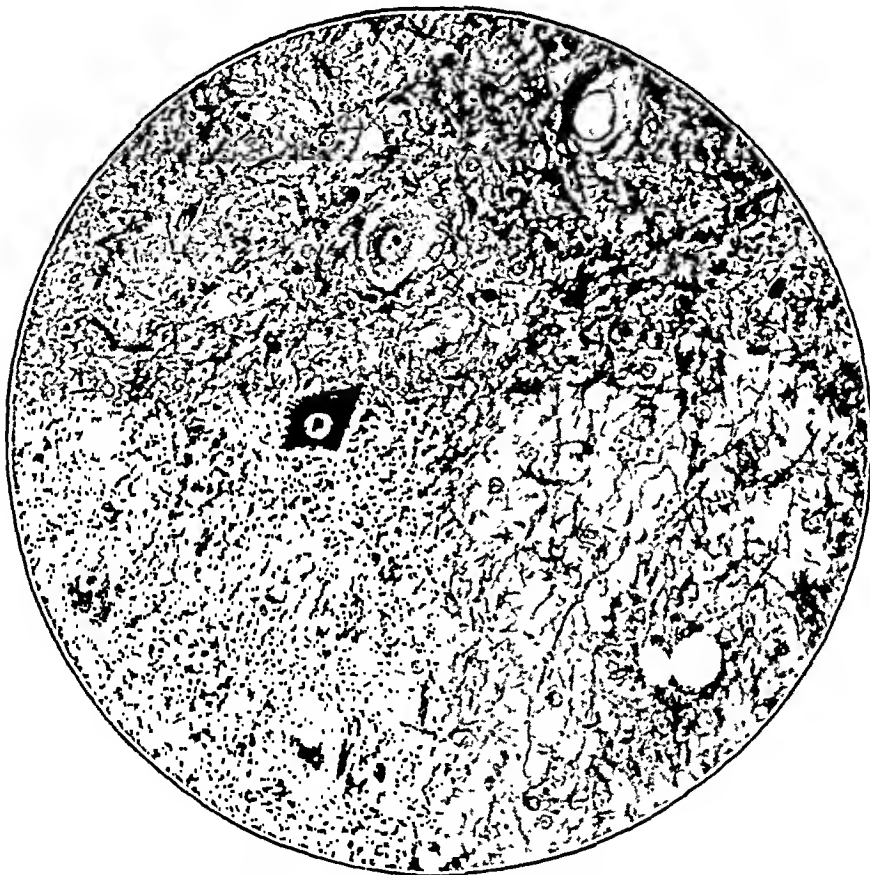


Fig. 13.—Photomicrograph, $\times 275$, showing changes in the dentate nucleus; Weigert stain. In the lower right quadrant there is an area of focal necrosis in which most of the myelin sheaths are lost. Two ganglionic cells immediately adjacent to it have undergone karyolysis and partial cytolysis. A cell in the left lower quadrant has an eccentric nucleus; the dark staining cell in the center of the field is normal, and the cell above it stains lightly.

in all probability some relation exists between them. Warrington¹⁸ has carefully studied the structural alterations of nerve cells following injury to their processes. On cutting the posterior spinal nerve roots in cats and monkeys he observed profound changes in the ganglionic cells of the posterior root; and on cutting the anterior spinal roots he observed marked changes in the corresponding cells of the anterior horn of the spinal cord. *The results enabled him to accept*

18. Warrington: Jour. Physiol., 1898, xxiii, 112.

as a general law that in a cell loss of continuity of its processes is followed by definite structural changes. He reviews the work of Marinesco, Lomy, Ballet, Munzer and Wiener to show that nerve cells undergo profound changes in consequence of disturbances of the vascular system; and he cites Nissl to the effect that nerve cell alterations may appear within twenty-four hours after injury to the processes.

Round Cell Infiltration: This lesion occurs less uniformly than any of the previously described lesions, and is generally associated with hemorrhages occurring near or adjacent. The infiltrated area differs from the hemorrhages in that while the hemorrhages are found sharply limited and round, the infiltrated areas tend to be diffuse and bear no special relation to the blood vessels.

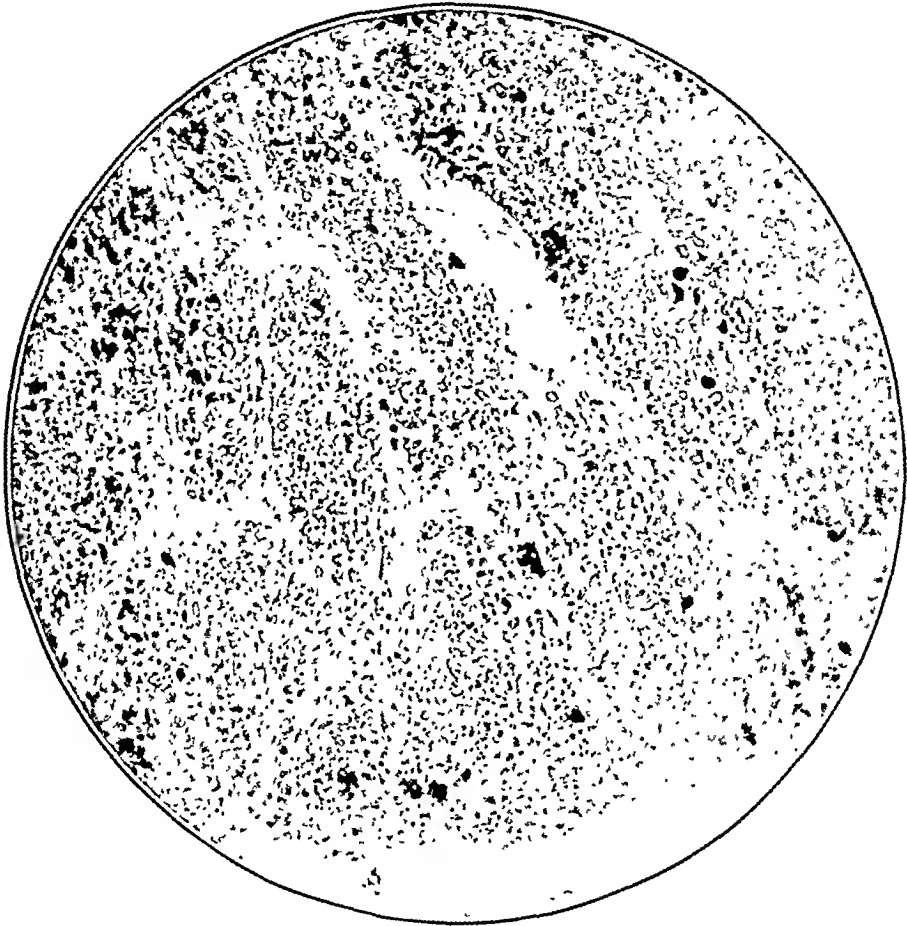


Fig. 14.—Photomicrograph, $\times 110$, showing degenerated nerve fiber sheaths, Marchi preparation, in the fasciculus anterolateralis of the spinal cord at the level of the decussatio pyramidum.

Changes in the Spinal Tracts: To determine what, if any, were the effects of the various lesions of the cerebellum and cerebrum on the pathways of the spinal cord, a block of cord was prepared by a slight modification of the Marchi method for degenerated myelinated fibers. This section was taken at the level of the decussatio pyramidum, and contains in the dorsal funiculus the fasciculus gracilis and the fasciculus cuneatus and their nuclei, of which a few fibers from the nucleus of the fasciculus cuneatus pass anteriorly to form the lower border of the medial lemniscus. In the funiculus lateralis there are the fasciculus lateralis proprius, the fasciculus cerebellospinalis of the Bash anatomical nomenclature, properly called the *tractus spinocerebellaris dorsalis* by Herrick¹⁹ and others, and the fasciculus anterolateralis, which includes the tractus

19. Herrick: An Introduction to Neurology, 1915, Chap. 8.

spinocerebellaris ventralis, the spinal lemniscus of Herrick or the tractus spinothalamicus of Cunningham,²⁰ the tractus rubrospinalis. In the funiculus ventralis there is the narrow bundle of the fasciculus proprius ventralis on either side and the rather large pyramids of the fasciculus cerebrospinalis, which cross the midline and deflect the anterior sulcus. The spinal V tract is lateral to the substantia gelatinosa Rolandi, and there are portions of the dorsal and ventral spinal roots attached.

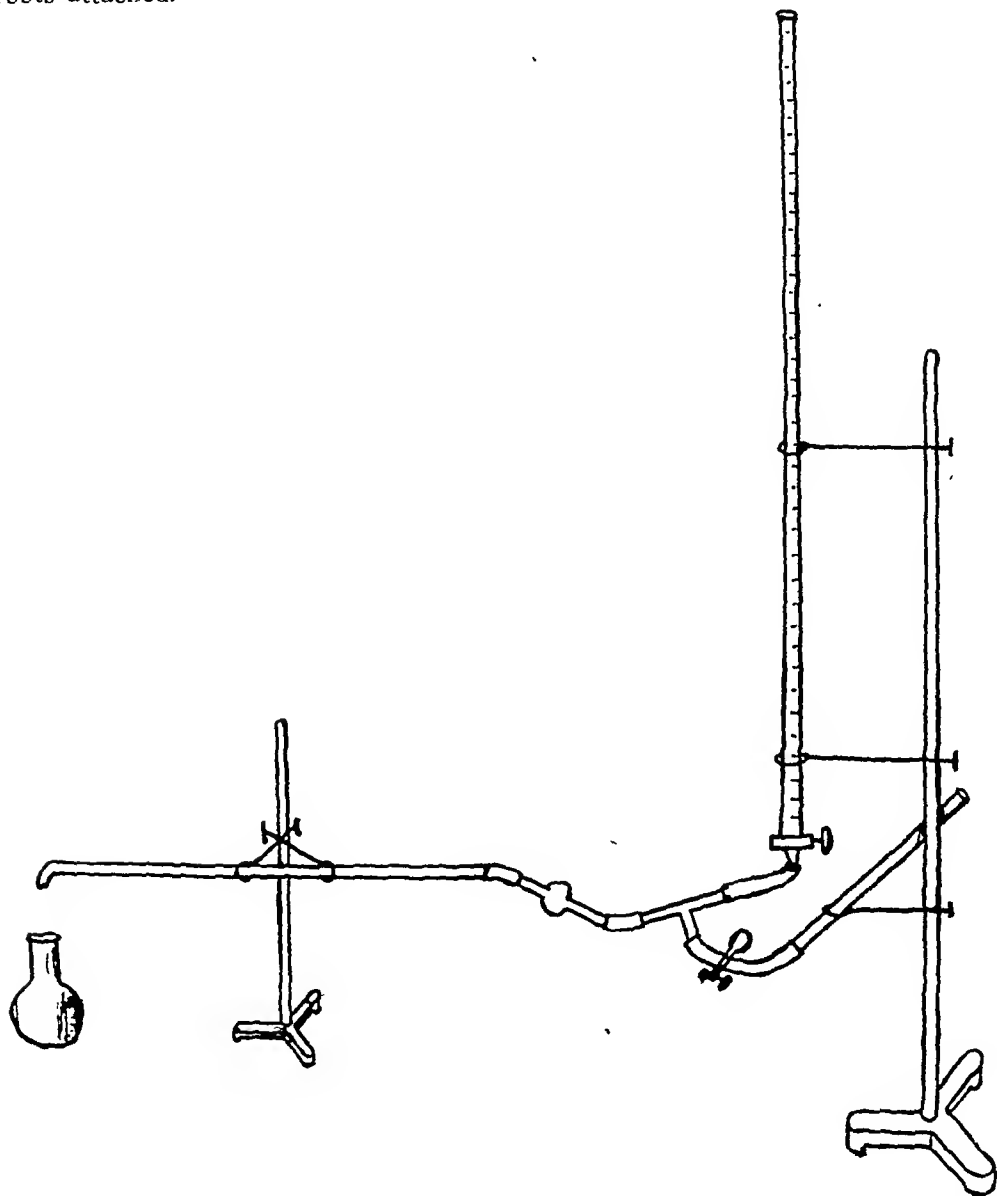


Fig. 15.—Apparatus, diagrammatic, used in studying viscosity and capillary resistance.

In the funiculus ventralis, there are numerous degenerated fibers scattered among the normal fibers. The degenerated fibers form about 1 to 2 per cent. of the total number. They are uniformly distributed throughout the funiculus. In the funiculus lateralis, both in the ascending and the descending tracts, and in the spinal V tract there are degenerated fibers (Fig. 14); the number in

20. Cunningham: Text Book of Anatomy, New York, 1909, p. 468.

this funiculus is not so large as in the funiculus ventralis and the largest numbers occur in the fasciculus spinocerebellaris. In the funiculus dorsalis the degenerated fibers are present in about the same proportion as in the funiculus ventralis, and in the adjacent portions of the spinal roots a moderate number of degenerated fibers are present. The presence of degenerated fibers in the descending pathways was expected after demonstration of frequent nerve destruction at the higher levels, and their presence in the ascending pathways was anticipated. In view of the wide and uniform distribution of the lesions in those parts of the central nervous system examined it seemed not unlikely that they should also occur in other parts. The demonstration of degenerated fibers in the spinal roots and ascending pathways is strongly suggestive of lesions in the lower part of the cord and the more peripheral nerves, that were not available for study.

CORRELATION OF CLINICAL AND ANATOMICAL FINDINGS

In attempting to correlate these lesions with the clinical symptoms, it first becomes necessary to establish the alterations in the physiologic pathways of the central nervous system. In view of the various descriptions given to these tracts by authors, we shall for uniformity follow the nomenclature and descriptions given in chapters 8 and 9 of Herrick's *Introduction to Neurology*. It is not essential to correlate every observed lesion with these tracts. It is sufficient simply to establish an alteration of each of the constituent neurons, namely, the peripheral sensory neuron of the first order, the central neuron of the second order, etc.

In the exteroceptive conduction paths there are at the level of the neurons of the first order degenerated fibers in the dorsal spinal root; of neurons of the second order degenerated fibers in the spinal lemniscus; of neurons of the third order hemorrhage and destruction of nerve fibers in the internal capsule and cerebral cortex. In the lateral proprioceptive path there are of neurons of the first order degenerated fibers in the dorsal spinal root; of neurons of the second order degenerated fibers of the fasciculus anterolateralis superficialis and in the fasciculus spinocerebellaris, as well as destruction of nerve axons in the dentate nucleus. In the ventral proprioceptive conduction path there are at the levels of the neurons of the first order degenerated fibers in the fasciculus gracilis and cuneatus; of neurons of the second order hemorrhage and destruction of nerve fibers in the thalamic nucleus; of neurons of the third order hemorrhages and destruction of nerve fibers in the internal capsule and cortex. In the descending cerebrospinal pathways for voluntary muscular control there are at the level of neurons of the first order hemorrhage and destruction of nerve fibers in the motor areas of the precentral gyrus, also degenerated fibers in the fasciculus cerebrospinalis of the spinal cord; of neurons of the second order degenerated fibers in the ventral spinal roots. In the descending cerebellar pathway there are at the level of neurons of the first order destruction of nerve fibers in the dentate nucleus.

There is then in fat embolism of the central nervous system a condition that produces profound injuries to the anatomical pathways and centers which represent all types of functional connections.

To attempt to correlate the symptomatology with the observed lesions on the basis of the study of a single case is unsafe, irrespective of the completeness of the study. We can, however, point out certain relationships in which the observed lesions might have been contributory, if not the cause, of the clinical manifestations.

Delirium: Hirsch²¹ defines delirium as a psychopathic condition observed in the course of numerous diseases, characterized by incoherence in the chain of conceptions and by the appearance of symptoms of psychosensory and psychomotor irritation, in which the incoherence of conceptions is evident in the disconnected and confused speech and in the aimless movements of the patient. Gowers²⁷ defines delirium as a condition characterized by a loss of concord of the mental processes with the actual sensory impressions of the present or the memory of those of the past; in which the mental processes cease to correspond to reality, and these may be accompanied by false sensory images without sensory impressions, or perverted sensory impressions. We shall take the liberty of assuming that the observed focal lesions of the brain initiated stimuli to the regional tissues prior to causing their destruction. Fat embolism is an acute condition, in the clinical sense of the word, but nevertheless develops gradually over a period of from twelve to seventy-two hours or longer. *Delirium invariably comes in the early part of the clinical course*, shortly after the accident, and is followed by the comatose stage three to twenty-four hours later. There is then, in most instances, a short delirious stage followed by a longer comatose stage. The delirious stage is probably initiated by the stimuli from the fat emboli, which in the smallest capillaries are separated from the nervous tissue by only a thin wall, and the distention of which by the emboli might easily cause a mechanical irritation of the nervous tissue; or possibly it is the first effect of the asphyxia that follows occlusion of the capillaries. Further, it is not unlikely that the focal hemorrhages, focal edema, and focal necrosis also produce a mechanical irritation before causing destruction of the tissue. This is compatible with the commonly accepted phenomenon that many substances which cause a final inhibition of cell activity produce an initial stimulation. Cushing²³ has demonstrated that stimulation of the postcentral gyrus in the conscious patient resulted in cutaneous sensations which were subjectively localized as if coming from the skin, and that stimulation of the precentral gyrus²⁴ resulted in typical motor responses.

21. Hirsch: Ref. Handb. Med. Sciences, 1901, iii, 398.

22. Gowers: Diseases of the Nervous System, 1896, ii, 104.

23. Cushing: Brain, 1909, xxxii, 44.

24. Cushing: Jour. Am. Med. Assn., 1908, L, 847.

In the three blocks of tissue examined from the somatic muscular and cutaneous sensory areas of the postcentral gyrus, taken from the regions adjacent to the motor areas of the left and right legs and the motor arm area of the left cerebral hemisphere, multiple focal lesions are found; and in the auditory area of the superior and middle temporal gyri and in the sensory visual area of the calcarine fissure the lesions are observed. It is also quite likely that they are present in every other sensory area of the brain. *These lesions caused initial stimuli of the regional tissue and probably resulted in psychosensory irritation.* In the three blocks of tissue from the somatic motor areas of the precentral gyrus multiple lesions are observed. *These probably caused initial psychomotor irritation.* In the area of motor speech coordination in the triangular part of the inferior frontal gyrus multiple lesions are observed. The lesions in this area alone might account for incoherence of speech. Further, in the frontal and parietal association areas multiple lesions are also observed, which may have caused a loss of the stereognostic sense and incoherence in the chain of conceptions; and finally, similar lesions are observed in the great coordinating center, the cerebellum. That delirium may be caused by multiple focal lesions has been noted many times. Gowers states that among the organic lesions producing delirium is multiple degeneration. Hirsch states that delirium may arise in organic diseases of the brain as a sequel to minute hemorrhages, and Smith²⁵ describes punctiform hemorrhages in the morbid anatomy of delirium.

Coma: This does not permit of as careful an analysis as does delirium. Most writers regard it as a symptom occurring in a large variety of diseases, and as such there has been a reluctance to describe definite pathologic changes to it. Gowers²² defines coma as a prolonged loss of consciousness, in which the patient cannot be aroused and in which the reflexes of the limbs are decreased or lessened, accompanied by a general loss of muscular tone and by disturbance in the respiratory rate and rhythm. Mercier²⁶ describes coma as being associated with those cases in which there is a state of evident defect of consciousness, together with a tendency to death by asphyxia; it is accompanied by a paralysis, more or less complete, of the voluntary muscles and an incomplete paralysis of the visceral musculature; independent movements of the eyes may occur, and death may result from a failure of respiration. He regards coma as a late stage in the operation of the law of dissolution, in which the highest nervous processes, being the latest and least organized, are the first to disappear; and the lowest nervous processes, being the longest and most completely organized, are the last to disappear; this law being a reversal of the law of evolution. This analogy is very interesting from the phylogenetic point of

25. Smith, Allbutt and Rolleston: *System of Medicine*, 1910, viii, 899.

26. Mercier: *Brain*, 1886-7, ix, 467.

view and from the fact that it removes the phenomenon of coma from the phase of an accidental occurrence in disease and places it definitely in the working order of a great fundamental law; but it nevertheless does not aid in its analysis along anatomic-pathologic lines. We believe that irrespective of the cause of coma the functional alterations of the nervous system have anatomic-pathologic equivalents. Edema, hemorrhages, necrosis, among others, have been mentioned; these are present in fat embolism. We regard the wholesale injuries to the entire system of conduction pathways and the functional areas of the brain of greater significance. The violent delirium of the patient forbodes impending necrosis of the regional nervous tissue of the brain in fatally terminating cases of fat embolism; and this necrosis has been amply demonstrated throughout the central nervous system.

In attempting to prove a direct relationship between the brain changes and the clinical symptoms, it is evident that if similar lesions can be demonstrated in other diseases associated with delirium and coma, the relationship in fat embolism tends by analogy to become established. Accordingly a study was made of the literature of those diseases in which occlusion of the brain capillaries is likely to occur. This is true of all parasitic diseases in which free parasites circulate in the blood, and in certain diseases associated with embolus formation. The study has been partially successful; and while the results have not been as gratifying as was to be hoped, this is not to be taken as failure to establish the connections between the brain changes and the clinical manifestations in all these diseases, but rather to the limitations of our study.

In malaria of the so-called pernicious type an almost identical relation exists between the cerebral symptoms and brain changes. Clinically, delirium followed by coma has often been described. In Ewing's²⁷ study of nine cases of fatal malaria five of the patients developed delirium followed by gradually deepening coma, two went into coma without delirium, but the cause of death in these two was not shown to have been due to malaria. In one the probable cause of death was endocarditis, and in the other the diagnosis of malaria was only questionably established. The length of time that the patients lived after the appearance of these symptoms varied from a few hours to several weeks. Ewing concludes that the cerebral symptoms were due to the obstruction of the brain capillaries and the subsequent circulatory disturbances. The brains of persons dying of malarial coma have been described as edematous, hyperemic, discolored by pigment, and containing numerous punctate hemorrhages (Spiller²⁸). Microscopically, there is a massing of infected red blood cells and malarial

27. Ewing: *Jour. Exp. Med.*, 1901-5, vi, 119.

28. Spiller: *Am. Jour. Med. Sc.*, 1900, cxx, 629.

parasites in the capillaries, with occlusion of the vessels; occasionally there is thrombosis followed by secondary changes in the adjacent tissue. Emge²⁹ describes multiple small, well-defined, circular areas of necrosis about the capillaries which are filled with masses of red cells and parasites, in the brain of an old man found comatose in the street, and later shown to be suffering from pernicious malaria. In Ewing's series parasites were found in the capillaries of the brains of three patients.

In trichinosis a similar correspondence exists. Thompson³⁰ made a clinical study of fifty-two cases, in which there were two deaths, one patient dying from complications of lobar pneumonia and erysipelas; but in the other patient death was due to the trichina infection. This patient died in delirium with a respiratory rate of 60, pulse 132, high fever and an eosinophilia of 14 per cent. Herrick and Janeway³¹ report an outbreak in an Italian family in which the mother, after a week of mild symptoms, became delirious, with a temperature of 104, pulse 130 and a rapid respiratory rate. In trichinosis the parasites circulate freely in the blood according to Herrick and Janeway, also Packard,³² and as such may become emboli. Frothingham³³ tells of having found them in the brain tissue. The capillaries were occluded and some were broken through by the parasites, which then made their way into the brain substance, where they incited round cell infiltration and caused local destruction of tissue and punctate hemorrhages.

Armstrong and Mullally³⁴ report two fatal cases of filariasis that strongly suggest the presence of parasites in the brain, but unfortunately the brains were not examined. Both patients were young girls, who soon after admittance to the hospital developed a high fever, 103 and 104, the pulse became weak and rapid, 136 and 134 respectively; the respiratory rates were 24 and 60; both became delirious, then comatose, and died without regaining consciousness. Filarial parasites in the blood have been frequently demonstrated. Connal³⁵ found them in the blood of 25 per cent. of seven hundred Langos natives. Our efforts to find a specific instance in the literature where they have been demonstrated in the brain have not been successful thus far; but in view of their frequent and repeated demonstration in the blood it seems probable that a thorough search might meet with success.

Cerebral embolism from valvular endocarditis is frequently reported in the literature. A single instance by Peabody³⁶ will be

29. Emge: *Tr. Chicago Path. Soc.*, 1914, ix, 133.

30. Thompson: *Am. Jour. Med. Sc.*, 1910, cxl, 157.

31. Herrick and Janeway: *THE ARCHIVES INT. MED.*, 1909, iii, 263.

32. Packard: *Jour. Am. Med. Assn.*, 1910, lix, 1297.

33. Frothingham: *Jour. Med. Research*, 1906, xv, 483.

34. Armstrong and Mullally: *Surg., Gynec. and Obst.*, 1914, xix, 699.

35. Connal: *Jour. Trop. Med.*, 1912, xv, 5.

36. Peabody: *Med. Rec.*, New York, 1883, xxiv, 633.

cited, because it is typical for our purpose. The patient, a young man, suffered from palpitation of the heart, dyspnea, edema of the feet, shortness of breath, fluid in the pleural cavities; the apex beat was diffuse and there was a loud systolic murmur. On Oct. 20, 1883, he became restless and had incontinence. During the two following days the restlessness increased, and on October 22 he was quite delirious, so that he had to be restrained; morphin was administered, but it failed to quiet him. On October 24 the delirium subsided, he became quiet and was removed from the straight-jacket. He soon sank into a stupor, which gradually deepened, and he died on October 25 without regaining consciousness. On postmortem examination the basilar artery was seen to be plugged with emboli. The entire lumen of the vessel was obliterated. There was edema of the brain and the ventricles were dilated. In the mitral valve both cusps were markedly thickened and quite rough. On the roughened edges could be seen many little vegetations of fibrin and fibrous connective tissue. Peabody thinks that this was the origin of the numerous emboli in the cerebral vessels, and that the cerebral symptoms were coincident with the lodgment of the emboli in the brain.

TABLE 3.—A COMPARATIVE STUDY OF CEREBRAL EMBOLISM

Disease	Delirium	Coma	Observer	Emboli and changes in the brain	Observer
Fat embolism...	+	+	Scriba	+	Scriba
Endocarditis ...	+	+	Peabody	+	Peabody
Malaria	+	+	Ewing	+	Emge
Filariasis	+	+	Armstrong and Mullally	—	
Trichinosis	+	—	Thompson	+	Frothingham

The pathology of delirium and coma has not been definitely established. From the data in the literature, there is evidence indicating that they may be caused by a variety of anatomical lesions in addition to those mentioned. Hoch³⁷ has studied the brain of a man dying of delirium tremens, and finds alterations in the pyramidal cells of the cortex cerebri, no mention being made of alterations of fiber tracts or evidence of focal necrosis.

CONCLUSION

In view of the profound disturbance in the central nervous system produced by the secondary changes of fat embolism, it is reasonably safe to conclude that these multiple lesions are intimately associated with the clinical manifestations of delirium and coma.

In conclusion I wish to express my deep gratitude to Drs. H. Gideon Wells, C. Judson Herrick, E. R. LeCount and R. R. Bensley for their kind assistance in this study.

37. Hoch: *Am. Jour. Insan.*, 1897, liv, 589.

A CRITICAL CONSIDERATION OF SYSTEMIC BLASTOMYCOSIS

WITH NOTES ON CERTAIN SPECIAL FEATURES AND REPORT OF
FIVE CASES *

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The appearance of a disease in a locality in which it had seldom or never been recognized is of somewhat more than local interest, not only from the viewpoint of geographic distribution, but also from that of causation and of variation in type or manifestation. Particularly is this true of a disease which exhibits so marked a range of appearance and so much confusion in diagnosis as does the condition generally known in this country as blastomycosis. This infection, caused by an organism or group of organisms the different strains of which are evidently related to certain of the higher molds on the one hand, and to the torulae on the other, is one of the most important of the group of mycoses.

The localized skin disease produced by this type of parasite is widely distributed geographically and is not infrequently encountered. It is fairly easy of recognition and is quite well understood, particularly from the clinical point of view. Reports of generalized invasion, however, have been relatively infrequent and from few localities. The majority of recognized cases have occurred in the Chicago district, so that for a time it was referred to by many as Chicago disease. When the wide geographic distribution and frequent occurrence of the blastomycotic dermatitis is considered, however, one gains the impression that instances of more or less generalized invasion should occur more often than is indicated by the records. This rarity of reported systemic blastomycosis would seem to depend on two factors: first, that cases of skin infection seldom develop a generalized metastatic invasion; and second, that the majority of such generalized cases show pulmonary or other lesions primarily and are usually mistaken for tuberculosis. Recent literature indicates that the disease is becoming recognized as actually having a wide distribution.

The manner in which the cases which are the basis of the present discussion were recognized is quite illustrative of the difficulty in diagnosis. They were encountered at the Charity Hospital in New Orleans

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since the reorganization of the pathological department of that institution early in 1914, under the direction of Dr. C. W. Duval. Three of the cases were from the ward services of one of us. Case 1 was considered tuberculosis until routine microscopic study of the tissues was made. Shortly afterward two other similarly mistaken cases were found by an associate (Dr. T. D. Hurley), in histologic study of necropsy material. The first of these (Case 2) had been diagnosed pellagra and pulmonary tuberculosis, the other (Case 3), as lupus vulgaris and tuberculosis of lungs and lymph nodes. Case 4 had been treated for months as surgical tuberculosis and was recognized only when a piece of excised tissue was sent to the laboratory for examination. It was then observed clinically for some time and the organism cultivated. Permission for a necropsy could not be obtained. Case 5 was diagnosed as blastomycosis, but no opportunity had been had to cultivate the organism previous to the necropsy. The heart lesion in this case is believed to be unique.

Three collections of cases have appeared in the literature, the older being those by Hektoen¹ and Montgomery and Ormsby.² Since then Stober³ has added six more Chicago cases to the list. Only two of the cases included in these summaries are from European literature. That by Busse,⁴ in 1894, was the first recorded systemic invasion by such a fungus, while the other was recognized shortly afterward by Curtis⁵ in France. Since that time numerous other foreign reports have been made. As is also the fact in this country, many of these show confusion as to diagnosis and classification. This is true in spite of attempts to systematize the fungi, notably by Engler and Prantyl⁶ Brumpt⁷ and most recently in this connection by deBeurmann and Gougerot.⁸ Since it is impractical and of little value to attempt to collect and classify these or the even less definite South American, Asiatic and other reports, the tabulation herein to be presented has been confined to North American cases. For consistency, therefore, we have dropped the above-mentioned first cases included by previous authors.

By a careful review we have been able to collect a total of forty-two cases which, on account of dissemination of the lesions, have, in the broad classification of American authors, been termed systemic blastomycosis. The reports so collected are shown in Table 1. For

1. Hektoen, L.: Jour. Am. Med. Assn., 1907, xlix, 1071.

2. Montgomery, F. H., and Ormsby, O. S.: ARCH. INT. MED., 1908, ii, 1.

3. Stober, A. M.: THE ARCHIVES INT. MED., 1914, xiii, 509.

4. Busse, O.: Centralbl. f. Bakteriöl., 1914, xvi, 175.

5. Curtis, F.: Ann. de l'Inst. Pasteur, 1896, x, 449.

6. Engler and Prantyl: *Natürliche Pflanzenfamilien*, 1897, Part 1, Section 1 (quoted by Whitman and by MacNeal and Taylor).

7. Brumpt, E.: *Précis de Parasitologie*, Paris, 1910 (quoted by MacNeal and Taylor and others).

8. De Beurmann and Gougerot, *Les Nouvelles Mycoses*, Paris, 1911.

the sake of completeness we will add like summaries of the five cases to be described. The addition of these to the cases already on record makes a total of forty-seven American reports.

In addition to the cases listed above, there have been found several which were either too incompletely studied and reported properly to be here included, or were but indirectly referred to. For instance, Montgomery and Ormsby give details of five "probable cases." These Stober did not consider, though he did remark that he knew of seven unreported instances of similar invasion. Hutchins⁹ reported briefly two cases as possibly blastomycosis. Campbell¹⁰ speaks indefinitely of a second case from the South as reported from Texas, the first being Case 22 above. We have been unable to find the report referred to. He also states that Hutchins was now convinced that his two cases had been blastomycotic. Sheperd¹¹ in discussion referred to another case in Montreal, positively established at necropsy, which he had seen by the courtesy of a confrère. Breen¹² somewhat superficially describes cases of a yeast infection, referred to as saccharomycosis, which we shall discuss in another connection.

In Table 1 there is a group of reports of blastomycotic infections to which we would call particular attention, since it is our conviction that they are erroneously and unsatisfactorily classified as generalized or systemic. We refer to cases of deep-seated lesions, whether subcutaneous, muscular or of bones or joints, single or multiple, in which the lungs and other viscera escape involvement. In these the infection is confined to a part or to parts in such a manner as to be often amenable to surgical treatment in conjunction with other measures. In the table summary, Cases 2, 11, 21, 23, 24, 25 and 41 seem more or less logically classed as distinct from the typical generalized condition in which the deeper organs are involved and in which medication is usually futile. Extension, when it occurs in these cases, is either direct or by way of the lymphatic channels, and recovery usually occurs under proper treatment. The first of these, Case 2, reported by Gilchrist (Case 4 of Hektoen), was subcutaneous only and the patient recovered under local and general treatment. In Case 11, reported by Herrick, recovery followed after prolonged extensive involvement. Case 21, reported by Brewer and Wood, was a localized infection involving the vertebral column. Two operations were performed and the patient recovered. In Case 23, reported by Fowler, the breast of a married woman of 45 years was extensively involved

9. Hutchins, M. B.: *Jour. Am. Med. Assn.*, 1898, li, 1868.

10. Campbell, J. L.: *Atlanta Jour.-Rec. Med.*, 1909, xii, 308.

11. Sheperd, F. J., and Rhea, L. J.: *Jour. Cutan. Dis.*, 1911, xxix, 588, and personal communication.

12. Breed, L. M.: *THE ARCHIVES INT. MED.*, 1912, x, 108.

TABLE 1.—HISTORY OF REPORTED NORTH—

Case No.	By Whom Reported	Where Reported	Locality	Sex	Age	Duration of Illness
1	Montgomery, F. H.	Jour. Cutan. Dis., 1901, xix, 318; Ibid., 1907, xxv, 393	Ill.	♂	33	7 mo. ulcer.... 9 mo. systemic
	Walker, J. W., and Montgomery, F. H.	Jour. Am. Med. Assn., 1902, xxxviii, 867				
2	Gilchrist, T. C.	Brit. Med. Jour., 1902, ii, 1321	Md.	♂	28	4 years.....
3	Ormsby, O. S., and Miller, H. M.	Jour. Cutan. Dis., 1903, xxi, 121; Jour. Am. Med. Assn., 1903, xli, 1074	Ill.	♂	56	8 months.....
4	Cleary, J. H.	Medicine, 1904, ix, 818; Tr. Chicago Path. Soc., 1904, v, 105	Ill.	♂	23	Several months
5	Eisendrath, T. H., and Ormsby, O. S. LeCount, E. R., and Myers, J.	Jour. Am. Med. Assn., 1905, xlv, 1045 Jour. Infect. Dis., 1907, iv, 187; Tr. Chicago Path. Soc., 1907, vii, 49	Ill.	♂	33	2½ years.....
6	Bassoe, P.	Jour. Infect. Dis., 1906, iii, 91	Ill.	♂	17	15 months.....
7	Irons, E. E., and Graham, E. A.	Jour. Infect. Dis., 1906, iii, 666	Ill.	♂	47	10 months.....
8	Christensen, C., and Hektoen, L.	Jour. Am. Med. Assn., 1906, xlvii, 247	Ia.	♂	28	20 months.....
9	Christensen, C., and Hektoen, L.	Jour. Am. Med. Assn., 1906, xlvii, 247	Ia.	♂	58	2 years.....
10	Coley, W. B., and Tracy, M.	Jour. Med. Research, 1907, xvi, 237	N. Y.	♂	27	10 months.....
11	Herrick, J. B.	Jour. Am. Med. Assn., 1907, xlix, 328	Ill.	♀	24	2½ years.....
12	Montgomery, F. H.	Jour. Cutan. Dis., 1907, xxv, 393	Ill.	♂	32	2 years.....
13	Ormsby, O. S.	THE ARCHIVES INT. MED., 1908, ii, 1	Ind.	♂	33	2½ years.....
14	Irons, E. E.	THE ARCHIVES INT. MED., 1908, ii, 1	Ill.	♂	20	1½ years.....
15	Hyde, J. N., and Montgomery, F. H.	THE ARCHIVES INT. MED., 1908, ii, 1	Ill.	♂	24	8 years (?).....
16	Oswald	THE ARCHIVES INT. MED., 1908, ii, 1	Ill.	♂	Adult	(?).....
17	Krost, M. A., Stober, A. M., and Moes, M. J.	Jour. Am. Med. Assn., 1908, i, 184; THE ARCHIVES INT. MED., 1914, xiii, 557; partially reported, Ibid., 1908, ii, 1	Ill.	♂	42	6 months.....
18	Churchill, T., and Stober, A. M.	THE ARCHIVES INT. MED., 1914, xiii, 568; partially reported, Ibid., 1908, ii, 1	Ill.	♂	39	4 months.....
19	Lewison, M., and Jackson, H.	THE ARCHIVES INT. MED., 1914, xiii, 575; partially reported, Ibid., 1908, ii, 1	Ill.	♂	17	13 months.....
20	Myers, H. J., and Stober, A. M.	THE ARCHIVES INT. MED., 1914, xiii, 585; partially reported, Ibid., 1908, ii, 1	Ill.	♂	Adult	9 months.....
21	Brewer, G. E.	Proc. New York Path. Soc., 1907-08, vii, 54	N. Y.	♂	20	6 months.....
	Brewer, G. E., and Wood, F. C.	Ann. Surg., 1908, xlviii, 889				
22	Fontaine, B. W., Haase, M., and Mitchell, R. H.	THE ARCHIVES INT. MED., 1909, iv, 101	Tenn.	♀ (white)	27	5 months.....

* The type of organism was ordinary budding in all cases except as follows: Not determined in Nos. 12, 14, 16, 17, 24, 25, 26, 28, 30, 39, 40 and 41; spores are also possibly produced in No. 5.

—AMERICAN CASES OF SYSTEMIC BLASTOMYCOSIS*

Necropsy	Distribution of Lesions	Remarks
Complete	Lungs, liver, spleen, kidneys, cutaneous and subcutaneous	This is Case 3 of Montgomery and Ormsby's series
.....	Multiple cutaneous and subcutaneous.....	Recovery (Case 4 of M. and O.)
Complete	Lungs, spleen, kidney, pancreas, larynx, trachea, pleura, cutaneous and subcutaneous	Case 5 of M. and O.
Complete	Lungs, kidney, adrenal, liver, cutaneous and subcutaneous	Microscopically found in myocardium and spleen (Case 6 of M. and O.)
Complete	Lungs, bronchial lymph nodes, kidney, liver, cerebrum, cerebellum, vertebrae, spinal cord, bones, cutaneous, (colon ?)	Unusual form in cerebellum (Case 7 of M. and O.)
Complete	Lungs, mediastinal lymph nodes, vertebral, cutaneous and subcutaneous	Case 8 of M. and O.
Complete	Lungs, spleen, kidney, vertebrae and other bones, cutaneous and subcutaneous	Cultivated from kidney, though none in smears or sections (Case 9 of M. and O.)
None	Widespread cutaneous and subcutaneous.....	Case 10 of M. and O.
None	Cutaneous, subcutaneous and muscular.....	Skin only examined. Sputum negative. Early later tubercle bacilli without blastomyces (Case 11, M. and O.)
None	Lungs, cutaneous (rectum ?).....	Originally called coccidioidal granuloma by authors (Case 12, M. and O.)
.....	Cutaneous, bone	Recovery (Case 13, M. and O.)
Partial	Lungs, spleen, appendix, inguinal lymph nodes, peritoneum, thigh, cutaneous	Several forms observed. Very pathogenic (Case 14, M. and O.)
.....	Lungs, knee, cutaneous.....	Very ill at time of report (Case 15 of M. and O., previously unreported.)
None	Lungs, popliteal, cutaneous.....	Organism not specified (Case 16 of M. and O., previously unreported.)
.....	Lungs (?), cutaneous, thigh, knee.....	Organism not specified (Case 17 of M. and O., previously unreported.)
By Dr. A. W. Evens (Unreported)	Cutaneous, joints, vertebrae, spinal cord, "general" in organs	Organism not specified (Case 18 of M. and O., previously unreported.)
Complete	Lungs, kidney, spleen, cerebrum, cerebellum, pleura, lymph nodes, prostate, bone, cutaneous and subcutaneous	Partially reported by M. and O. Fully reported by authors.
Complete	Lungs, pleura, kidney, prostate, bone, eye, cutaneous and subcutaneous	Partially reported by M. and O. Fully reported by authors.
Complete	Lung, bone, brain, lymph nodes, cutaneous and subcutaneous	Partially reported by M. and O. Fully reported by authors.
Complete	Lungs, liver, spleen, pancreas, kidney, cerebrum, cerebellum, bone, cutaneous and subcutaneous	Partially reported by M. and O. Fully reported by authors.
.....	Vertebrae, muscles, subcutaneous.....	No mycelia in cultures; operation; recovery
Extent not specified	Lungs, spleen, cutaneous.....	First case from South.

TABLE 1.—HISTORY OF REPORTED NORTH AMERICAN—

Case No.	By Whom Reported	Where Reported	Locality	Sex	Age	Duration of Illness
23	Fowler, R. H.	Long Island Med. Jour., 1909, iii, 423	N. Y.	♀	45
24	Fowler, R. H.	Long Island Med. Jour., 1909, iii, 423	N. Y.	♂	30
25	Campbell, J. L.	Atlanta Jour.-Rec. Med., 1909, xii, 308	Ga.	♂	31	17 years.....
26	Rusk, G. Y.	Proc. New York Path. Soc., 1910-11, x, 48	N. Y.	♀	63	?.....
	Rusk, G. Y., and Farnell, F. J.	Univ. California Publ. Path., 1912, ii, 47				
27	Sheperd, F. J., and Rhea, L. J.	Jour. Cutan. Dis., 1911, xxix, 588, and personal communication	Prov. Que. (Montreal)	♂	25	9 months.....
28	Ravogli, A.	Lancet-Clinic, 1911, cv, 489	Ohio	♂	31	4 years.....
29	Washburn, R. G.	Jour. Am. Med. Assn., 1911, lvi, 1095	Wis.	♂	70	14 months.....
30	Rusk, G. Y., and Farnell, F. J.	Univ. California Publ. Path., 1912, ii, 47	N. Y.	♂	57	2 years.....
31	Boughton, T. H., and Clark, S. N.	THE ARCHIVES INT. MED., 1914, xiii, 594	Ill.	♂	21	14 months.....
32	Boughton, T. H., and Stober, A. M.	THE ARCHIVES INT. MED., 1914, xiii, 599	Ill.	♂	39	?.....
33	Jackson, H.	THE ARCHIVES INT. MED., 1914, xiii, 607	Ill.	♂	Adult	1 year.....
34	Beehtel, R. E., and LeCount, E. R.	THE ARCHIVES INT. MED., 1914, xiii, 609	Ill.	♂	38	7 months.....
35	Riley, F. B., and LeCount, E. R.	Jour. Cutan. Dis., 1903, xxi, 121; Jour. Am. Med. Assn., 1903, xli, 1074	Ill.	♂	31	6 months.....
36	Eisenstaedt, J. S., and Boughton, T. H.	THE ARCHIVES INT. MED., 1914, xiii, 617	Ill.	♂	19	10 months.....
37	Shaffner, P. F.	THE ARCHIVES INT. MED., 1914, xiii, 621	Ill.	♂	30
38	Hill, H. P., and Dickson, E. C.	California State Jour. Med., 1914, xii, 120	Calif.	♂	28	1 year.....
39	Dickson, E. C.	California State Jour. Med., 1914, xii, 120	Ill. and Calif.	♂	Adult	1 year ?.....
40	Powers, C. W.	Ann. Surg., 1914, lix, 815; personal communication	Colo.	♂	51	3 years.....
41	Hildreth, E. R., and Sutton, A. C.	Jour. Am. Med. Assn., 1914, lxiii, 2289	P. R.	?	?	?.....
42	LeCount, E. R.	Bull. Johns Hopkins Hosp., 1915, xxvi, 315	Ill.	♂	26	1 year ?.....

AUTHORS' CASES

Case No.	Charity Hospital Series	Sex	Color	Age	Duration	Neeropsy
43	1	♂	Colored	36	7 months	Complete
44	2	♂	Colored	18	10 months	Complete
45	3	♂	Colored	36	7 months	Complete
46	4	♂	White	32	2½ years	None
47	5	♂	White	61	1 year	Complete

Necropsy	Distribution of Lesions	Remarks
.....	Breast, rib	Organism not specified; operation; recovery
.....	Neck (multiple abscesses), conjunctiva.....	Organisms not specified; infection spreading at time of report
.....	Bones, cutaneous and subcutaneous, inguinal lymph nodes, etc.	Operations; infection spreading at time of report
Complete	Lung, brain, meninges.....	Organisms in this and Case 29 called oidium by authors
Extent not specified	Cutaneous and subcutaneous, bones, etc., lungs, spleen, liver, pleura, peritoneum, kidney, adrenal, prostate, esophagus	Discussed a second case not in his service
Extent not specified	Cutaneous and subcutaneous, tongue, tonsils, retropharynx, bone, pleura, diaphragm	Speaks of "spores" but differentiates coccidioidal granuloma
Extent not specified	Cutaneous, bones, joints, retropharynx.....	
Complete	Lung, kidneys, brain, meninges.....	As in Case 25
Limited	Lungs, bronchial lymph nodes, spleen, liver, bones, cutaneous and subcutaneous	
.....	Lungs, cutaneous and subcutaneous.....	Vaccine treated; improved and discharged after one year
.....	Lungs, cutaneous and subcutaneous.....	Discharged on request; unimproved
Complete	Lung, liver, spleen, kidney, adrenal, brain, cutaneous and subcutaneous, bone and lymph nodes	
Complete	Lung, spleen, liver, brain, prostate, peritonsillar tissues, pleura, lymph nodes, bone, epididymis, cutaneous and subcutaneous	
Complete	Lung, pleura, vertebrae, psoas abscess, bone, cutaneous and subcutaneous	
.....	Lung (?), bone, cutaneous and subcutaneous.....	Disposition of case not indicated
Complete	Lungs, larynx, kidney, testicle, epididymis, cutaneous, subcutaneous and bones	First case of true blastomycosis in California
Report indefinite	"Widespread" visceral lesions and destruction of bones	
Report indefinite	"Advanced lesions of chest, abdomen and joints"....	Necropsy performed by Dr. J. A. Wilder and reported as blastomycosis
.....	Subcutaneous, lungs (?).....	Small forms of organisms described; recovered
Complete	Lungs, lymph nodes, spleen, kidney, pancreas, pericardium (heart), peritoneum and cutaneous	Pericardial lesion described as retrogressive lymphatic blastomycosis

AUTHORS' CASES

Distribution of Lesions	Remarks
Lung, spleen, liver, pancreas, pleura	
Cutaneous and subcutaneous lungs.....	Unusual budding in skin complicated by pellagra (?) and pulmonary tuberculosis
Lungs, liver, kidneys, lymph nodes, cutaneous and subcutaneous	
Lungs, ribs, vertebrae, spinal cord, cutaneous and subcutaneous	
Lung, heart, pericardium, liver, brain, bones, cutaneous and subcutaneous	Diagnosed cutaneous blastomycosis by Dr. H. E. Henage about eight years before death

and an underlying rib was invaded. The patient is reported as having recovered after operation. Fowler's second case (Case 24) was also still localized at the time of report, but was said to be spreading in spite of treatment. In Case 25, reported by Campbell, the infection was of seventeen years' duration and was confined to the leg. In spite of operative interference it was continuously spreading, apparently by the lymphatics. Case 41, reported by Hildreth and Sutton from Porto Rico, was primarily subcutaneous. The lungs were perhaps involved, but this was not proved. The patient recovered under medical treatment.

When, as in these cases, the blastomycotic infection is limited to an extremity or to the superficial tissues elsewhere, the condition can often be ameliorated and perhaps cured by surgical interference, aided by proper medication. We would direct attention to the much-used analogy in tuberculosis, which infection may be cutaneous, as lupus vulgaris, systemic, usually via the pulmonary tissues, or a deep-seated tuberculosis, in which the generalization of the infection may be avoided by proper measures. Therefore, in view of the limited extent of infection, the more frequent spread by way of the lymphatics, the indicated treatment and the better prognosis we would prefer to distinguish these cases and, rather than to attempt a new term, would refer to them as cases of surgical rather than of systemic or generalized blastomycosis.

Geographically, the distribution of systemic blastomycosis is wide, almost general, though the cases ascribed to localities other than Illinois are scattered. Of the forty-seven collected cases, 53 per cent. are from that focus. Briefly, the distribution is as follows: Illinois twenty-four, New York six, Louisiana five, Iowa two, Maryland, Indiana, Tennessee, Georgia, Province of Quebec, Ohio, Wisconsin, California, Colorado (?) and Porto Rico one each.

While the focusing of the condition about Chicago may be due in part to the endemic establishment there of a particularly pathogenic fungus, or to the crowded, unhygienic living conditions of large numbers of people, particularly during the winter season, it may also be partly ascribable to an unusual efficiency of the medical profession there in recognizing the condition and to the interest which they have taken in it. The sparsity of reports from other communities, on the other hand, is undoubtedly in part due to its nonrecognition. This would seem to have been true of New Orleans, where five cases have been encountered in little more than one year.

More widespread occurrence of the condition than is indicated by present reports seems probable among communities where large numbers of people live massed in inadequate quarters, particularly where dampness and filth are the rule. This is particularly to be expected,

since it is evident that no one particular species of yeast mold fungus alone can be held responsible for the disease, but that a number of related molds may produce similar lesions. Stober investigated the living conditions of a number of the Chicago cases and made a very interesting and suggestive series of observation. His study of the molds, or mildew, found in such places points quite insistently to the adaptation of such fungi to parasitic life in the animal body. It had been our hope to extend these observations along other lines.

Studies of the cultural characteristics of different strains isolated, as well as the morphology of the organisms in the tissues of different cases, indicates that similar clinical conditions may arise from infection by different, though probably related, fungi. Certain morphological variations in tissues have been discussed in a separate publication.¹³ This was occasioned by the observation in a skin lesion from our Case 2 of myriads of organisms of various sizes, the majority so small as to suggest spore formation. This has been shown to be but the result of a modified, very rapid multiplication by budding. Whether this observation or the morphologic variations reported by LeCount and Myers,¹⁴ Smith¹⁵ and others necessarily indicates variation in type of organism may be questioned. They are probably but incidental and temporary modifications in reaction to unaccustomed biologic influences.

Careful cultural studies of the organisms usually encountered in blastomycetes have repeatedly been made and descriptions recorded. The monograph by Ricketts¹⁶ and the articles by Hamberger,¹⁷ Montgomery and Ormsby, Davis¹⁸ and particularly by Stober, are very replete. Cultures of the blastomyces were recovered from two of our cases. Neither these nor several other strains recovered from purely cutaneous infections have presented any feature not already thoroughly established.

The typical so-called blastomyces in the tissue lesion does not produce mycelia and does not form ascospores, but appears and persists in the form of more or less sclerotic, yeast-cell-like bodies which multiply entirely by budding. Isolated and cultivated artificially, it appears usually to be a mold of saprophytic type, growing at room temperature rather more readily than at 37 C., and usually very luxuriantly on bread and potato. Typically, it quickly ceases to grow in toruloid form and finally produces a white cottony mycelium.

13. Wade, H. W.: *Jour. Infect. Dis.*, 1916, xviii (in press).

14. LeCount, E. R.

15. Smith, A. J.: *Univ. Pennsylvania Med. Bull.*, 1909-10, xxii, 362.

16. Ricketts, H. T.: *Jour. Med. Research*, 1901, vi, 373.

17. Hamberger, W. M.: *Jour. Infec. Dis.*, 1907, iv, 201.

18. Davis, B. F.: *Jour. Infect. Dis.*, 1911, viii, 190.

Cultural variations are noted in practically all published reports. Such variations may be minor or apparently marked enough to establish different types. As a result of his observations of certain cultural features in a number of strains, Ricketts advocated an arbitrary subdivision of the group which was adopted for some time. It now seems demonstrated, however, that minor cultural variations are not sufficiently typical or constant, even after prolonged study, to use as a basis for subdividing the group. Montgomery and Ormsby emphasize this when they state that all of the described forms had been observed by them, at one time or another, in the same strain. Hamburger described a strain which had for years been cultivated in the usual mycelial form, but which finally underwent an unexpected modification, after which it persisted in growing in the toruloid form. Stober shows clearly what our own experience bears out, that Ricketts' types "represent different stages in the life history of the organism." He describes as quite frequent the separation of apparently pure cultures into two strains, one of which grows as hard, compact, white mycelial colonies which produce spores. One of us has obtained a similar subculture from a bouillon growth of the organism from our Case 4.

Somewhat different, it would seem, is that organism cultivated from the case studied by Brewer¹⁹ and by Brewer and Wood and Zinsser.²⁰ This organism never developed a mycelium, but persisted in growing as a torula over a considerable period of time. A possibly similar type of organism was found by Rusk and Farnell²¹ in the tissues of their cases. They describe, outside of the rather thin capsular membrane, a homogeneous, viscid capsule which served to bind, by a medium which showed delicate starlike intercapsular bands or adhesions, the organisms into zooglea masses. This is apparently an unusual feature in American blastomycosis and suggests the appearance described and pictured by Verity²² as seen in preparations of a nonmycelial blastomycetes. Rusk and Farnell considered their organisms oidia, though the cultural work necessary to establish such identity was not carried out. Breed,¹² as has been said, listed fifteen cases of various sorts from which cultures of torulous organisms had been obtained. Because of the incompleteness of the reports it cannot be asserted, but it seems quite probable, that Cases 11 and 14 of her series were instances of prolonged pulmonary infection, very possibly inaugurated secondarily by a toruloid organism of low pathogenicity. Her results with the yeast culture autobacterins and in agglutination reactions

19. Brewer, G. E.: *Proc. New York Path. Soc.*, 1907-08, vii, 54.

20. Brewer, G. E., and Wood, F. C.: *Ann. Surg.*, 1908, xlviii, 889 (containing a report of the bacteriologic study by H. Zinsser).

21. Rusk, G. Y., and Farnell, F. J.: *Univ. California Publ. Path.*, 1912, ii, 47.

22. Verity, R.: *Lo Sperimentale, ovvero giornale critico di medicina e chirurgia*, 1912, lxvi, 1.

indicate specificity. In this connection we may remark that two quite similar cases which have been observed by confrères in this city suffered pulmonary lesions evidently due to similar nonmycelium-producing organisms. One of these was rapidly fatal. The organism from this case was under observation by one of us for several months. Under no circumstance did it produce a mycelium.

It has become necessary to recognize, therefore, as most recently indicated by Wolbach,²³ two groups of these organisms aside from the *Coccidioides immitis*. This organism, though growing as a mold, never multiplies by simple budding either in the tissues or in cultures, and is considered by American authors, particularly by MacNeal and Taylor,²⁴ and also by Brown and Cummins,²⁵ as distinct from the blastomycetes. Few European authors have studied this organism, and the distinction is not always appreciated by them.

The first type in this subdivision is the true blastomyces or budding organism, the saccharomyces or torula, which does not produce mycelium in cultures. Among the cases due to such organisms were the early ones of Busse and Bushke, and of Curtis. These are of quite frequent occurrence in Europe. Here also may tentatively be placed the case of Brewer and possibly those of Breed, and according to Wolbach, those of Rusk and Farnell. If the two local cases referred to are reported they will fall into this group.

The second type is the usual American blastomyces of Gilchrist and Stokes,²⁶ zymonema of deBuermann and Gougerot, the causal agent of the great majority of cases tabulated herein. This organism, which has been given various specific names, multiplies in the tissues only by budding and grows culturally both by gemmation and mycelium formation. Further subdivision of this second group may ultimately be necessary as more strains are studied, but such exact identification entails much time and careful labor and is even then more or less uncertain.

In this connection attention may be called to the regrettable lack of uniformity in the nomenclature of these infections. It has repeatedly been asserted that the general term "blastomycosis" as applied to the clinical condition is inaccurate, unscientific and misleading, in that multiplication by gemmation in the lesion is but a phase in the life cycle of the majority of organisms implicated. Morphology of organisms in the lesions or exudates is without question an unsatisfactory basis of differentiation, although by this means the coccidioidal granuloma can be identified and it is agreed that

23. Wolbach, S. B.: Boston Med. and Surg. Jour., 1915, clxxii, 94.

24. MacNeal, W. J., and Taylor, R. M.: Jour. Med. Research, 1914, xxx, 261.

25. Brown, P. K., and Cummins, W. T.: THE ARCHIVES INT. MED., 1915, xv, 608.

26. Gilchrist, T. C., and Stokes, W. R.: Jour. Exper. Med., 1901, iii, 53.

a satisfactory classification must finally depend on both primary morphology and cultural manifestations of the organisms. By such means the group of organisms which do not produce mycelia can be separated with comparative ease. Subclassification of this group will depend on further observations. For example, instances of infection by a chromogenic (pink) torula are on record. The term *saccharomyces*, sanctioned by the usage of several authorities, is applied without regard to the action of these torulae on sugars. We would agree that for these organisms it is better to reserve the term "blastomyces." For the other type, which, though budding while in the tissues, produces mycelia on culture media, some more descriptive term, even the awkward "zymonema," would strictly seem preferable. "Oidium" cannot properly be used in view of the definition of that organism. A practical alternative might be to retain blastomyces for both groups and apply secondary modifying terms, even though both groups, as knowledge of the organisms increases, may ultimately be subject to further subdivision.

In the study of blastomycotic material from deep-seated, apparently uncontaminated lesions, coincidental occurrence of bacteria of one type or another has several times been observed. This is not a secondary bacterial contamination of open surface lesions, and is sometimes too widespread to be explained except on the ground of a general secondary invasion. When this invasion occurs, it is usually late in disease, when the resistance to invasion by, and multiplication of, bacteria of low infectivity is greatly lowered. Bacteria so found have been of various types. Hektoen found a diphtheroid in one of his cases and Zinsser observed a gram-positive coccus in a case studied with Brewer and Wood. In the eleven cases in Stober's collection were two in which such bacteria were found. In the first, Churchill and Stober (Table 1, Case 18), streptococci were isolated postmortem from the blood, pleural and peritoneal fluids and pus from the knee joint. The authors considered it a terminal invasion, as it was only met with a few days before death. In the case reported by Lewis and Jackson (Table 1, Case 19), *Staphylococcus albus* and *aureus* were isolated from the blood, pleural fluid, bile and pus from the abscesses of the knee joints, and from the left inguinal and right axillary regions.

In our own series similar secondary invaders were recovered from two of the three cases in which cultural work was carried out. In one (Case 1) there appeared at necropsy a gram-positive diphtheroid among the blastomycetes in lesions of the pancreas, lung and neck, though not present in pus from subcutaneous abscesses a few weeks before death. This diphtheroid proved nonpathogenic and is believed to be one of the numerous types of diphtheroids frequently recover-

able from tissue lesions.²⁷ Masses indicating antemortem dispersion of similar organisms which continued to develop after death were found in sections from Case 2. In Case 4 there was a definite, widespread invasion by a similarly associated, apparently saprophytic streptococcus. Many were found in pus freshly aspirated from unbroken abscesses. In some of the lesions there was also associated a gram-positive diphtheroid quite similar to that in Case 1. These bacteria not only caused no perceptible local or general reaction in the patients, but proved quite nonpathogenic to laboratory animals in every case.

The general features of systemic blastomycosis have been discussed repeatedly and in several instances quite thoroughly. No extensive review of the condition can be undertaken here. Briefly, it is typically a subacute or chronic infectious process, usually pulmonary at the outset, but characterized sooner or later by the development of subcutaneous abscesses, few or numerous, localized or widely dispersed over the body, and often involving bony structures, joints and surrounding soft tissues. The pulmonary lesions are at times pneumonic in type, but ultimately are proliferative, suppurative and destructive, and give many of the signs and appearance of tuberculosis.

The conditions determining infection are in general those which lower the resistance of the individual, but particularly the association with conditions encouraging mold growth, such as work or residence in damp, filthy quarters. The majority of cases have occurred in previously healthy adult males, usually living in reduced circumstances. As has been noted, Stober's investigation of the previous environment and living conditions of certain of the Chicago patients and his study of molds isolated from such places is very suggestive and, we believe, indicates the most probable source of the invaders.

Repeated inhalation of such fungi with their deposit on diseased lung surfaces, as in bronchitis, pneumonia or tuberculosis, may be sufficient to establish the infection. Whether some special sensitization must be developed, as held by Duval²⁸ with regard to leprosy, has not been shown, but seems doubtful. Stober recounts an incident in which a tube containing an old culture of a blastomyces was accidentally broken. Both individuals present at the time developed symptoms of more or less serious irritation of the respiratory tract, but these subsided in a few days. Possibly repeated inhalation would have established the disease. Whatever the mode of invasion usually is, factors such as adaptation of the organism to the host and susceptibility or lowered resistance on the part of the host must play important rôles. It is significant that practically all strains show very low pathogenicity for the ordinary laboratory animals.

27. Harris, W. H., and Wade, H. W.: *Jour. Exper. Med.*, 1915, xxi, 493.

28. Duval, C. W.: *New Orleans Med. and Surg. Jour.*, 1915, lxxvii, 1009.

The atrium of infection markedly influences the onset and course of the systemic disease. While it is sometimes impossible from a patient's history to determine whether the generalization of the organism occurred as a result of primary infection of the skin or of the lung, the evidence seldom points to the former mode of dissemination. Stober remarks that of the twenty-nine cases considered by him but three had been shown to develop from cutaneous lesions, and that in these such lesions had existed for from seven to twelve years. Case 5 of our series, we are informed, had been diagnosed as cutaneous blastomycosis about eight years previous to death. In Case 2, in which there was a complication of conditions, it is possible that the blastomycosis was primarily cutaneous. This cannot be asserted, however.

The onset varies in different cases. More commonly there is a history of a severe cold with cough and often expectoration of blood-streaked sputum, though in a few instances localized painful swelling of an extremity or joint as the result of secondary involvement was the first indication of the infection. These cases seem to develop by inoculation of the pulmonary tissues and are the most severe and rapidly fatal. Only rarely is the primary and principal lesion a cutaneous ulcer or subcutaneous abscess without evidence of lung involvement. It has been pointed out that in a few cases the infection, while ultimately deep seated and more or less extensive, seems not to have become systemic, but to have spread progressively by direct extension or by metastasis through the lymphatics without involving the deeper organs. The importance of distinguishing between truly systemic infections and such limited surgical lesions has already been discussed.

Once established, the course of the disease is usually subacute or chronic. Toxicity is seldom marked, even in extreme infections, so long as the infection is uncomplicated. The patient usually emaciates more or less rapidly, becomes extremely weak, and dies of exhaustion or some intercurrent event.

A most striking feature of advanced systemic blastomycosis is the wide range of organs that have been involved and the multiplicity of infection foci, not only in the same tissue, as, for instance, the bones, but also in the different tissues and organs. It has been thought of interest to arrive at an accurate conclusion regarding the frequency with which the different organs have been affected. In doing this it is necessary to consider only those cases in which complete postmortem examinations have been made and recorded. From the foregoing Table 1 it may be seen that among the forty-two cases collected from the literature, but twenty-three included sufficient data for this purpose. To these are now added the four necropsied cases of our series at the Charity Hospital, making a total of twenty-seven postmortems.

Table 2 shows the distribution of lesions in the different organs of these cases.

TABLE 2.—DISTRIBUTION OF LESIONS IN NECROPSIED CASES

	Collected, 23 Cases	Charity Hos- pital, 4 Cases	Total, 27 Cases	Per Cent. of Total
1. Lungs	22	4	26	96
2. Skin, etc.	21	3	24	89
3. Bone	15	1	16	59
4. Spleen	13	1	14	52
5. Kidneys	13	1	14	52
6. Liver	8	3	11	41
7. Lymph nodes	9	1	10	37
8. Brain, meninges, etc...	8	1	9	33
9. Pleura, etc.	7	1	8	29.5
10. Prostate	4	..	4	15
11. Retropharynx	3	..	3	11
12. Heart	2	1	3	11
13. Peritoneum	3	..	3	11
14. Pancreas	2	1	3	11
15. Adrenal	3	..	3	11
16. Muscles, without other involvement	2	1	3	11
17. Larynx	2	..	2	7.5
18. Pericardial cavity	1	1	2	7.5
19. Intestinal tract	2 (?)	..	2	7.5
20. Epididymis	2	..	2	7.5
21. Eye	1	..	1	4
22. Tongue	1	..	1	4
23. Tonsils	1	..	1	4
24. Trachea	1	..	1	4
25. Esophagus	1	..	1	4
26. Diaphragm	1	..	1	4
27. Testicle	1	..	1	4
			169	

From the list given in Table 2 the high frequency of involvement of both lungs and skin may be seen. The bones, spleen, kidney, liver and lymph nodes follow in order, the first three being affected in 50 per cent. or more of cases. It is interesting that the brain and meninges were involved in one third of this group of twenty-seven cases and the vertebral column in six, or 12.7 per cent., out of the total of forty-seven cases tabulated. Myocardial invasion is quite infrequent, and the unique lesions in the heart of our Case 5 have been reported by Hurley²⁹ from these laboratories.

Table 2 also demonstrates the wide range of possible organ infection in blastomycosis, and emphasizes the multiplicity of such foci.

29. Hurley, T. D.: Jour. Med. Research, 1916, xxxiv (in press).

In the twenty-seven cases there was a total of 169 organ foci, or an average invasion of 6.25 organs per case. This of course does not consider the number of foci in a single tissue, which often attain a considerable number in such tissues as the bone and skin.

Little can be added from careful study of our cases to the generally understood pathology of the disease. As may be inferred from our description of the condition of the lung in the report of our Case 1, lesions at times may be exudative in type, producing the blastomycotic pneumonia pictured by Mallory³⁰ but sooner or later become proliferative and destructive. In some cases miliary proliferative lesions very closely simulating tuberculosis occur from the start. Lesions of this type are also very numerous in the liver of Case 1. In other lesions the reaction may be persistently suppurative in nature. This is exemplified by the kidney lesion in Case 3. It sometimes appears as if the tendency in different cases is either toward the proliferative lesion throughout or toward the suppurative. This may depend on the strain of the fungus, the reaction of the host and the occurrence of general secondary invasion.

An interesting feature of the histopathology of blastomycosis is the great variability in the number of organisms present and in their distribution within the lesion. In the usual lesion they are found within giant cells and free among the tissue cells, though in some sections they may be found entirely within the giant cells. Occasionally, on the other hand, none can be found within giant cells, though these may be present at times in considerable numbers. In numbers the variability is still more striking. Frequently one finds large numbers of the organisms present; these may even occasionally be the predominant cell in the field. On the other hand, the organisms may be scarce and difficult to determine. Occasionally one finds a diagnosis reported as made, or at least strongly suggested, though no blastomycetes whatever are found in the lesion.

In our Case 1 the lung lesions showed the characteristic organisms sometimes in great numbers. In the spleen, on the other hand, extensive lesions were found in which but a few organisms can be detected on careful search, and these few sclerotic cells appear much degenerated. Here are extensive areas showing widespread necrosis (necrobiosis), with little leukocytic infiltration and no fixed-tissue proliferation. No tubercle bacilli were found. An apparently similar lesion is spoken of by Powers, reported by Whitman, as a coagulation necrosis, and other authors, as Montgomery, Case 12, have spoken of like conditions. The organism in Powers' case, however, has been shown by MacNeal and Taylor to have been the *Coccidioides immitis*.

30. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia and London, 1914, p. 231.

In the liver of our case in question are very numerous miliary areas of primarily proliferative nature, with infiltration of endothelial leukocytes, and central necrosis. Here, too, very few blastomycetes can be found. Explanation of such lesions have never been entirely satisfactory. Were the organism a strong toxin-producer and capable of causing considerable areas of toxic necrosis from small or distant collections of the yeast cells, such lesions might be expected. The appearance of the usual type of lesion does not give credence to this, nor do the results of cultural study and animal inoculation. Another possibility is that these areas of mass necrosis are in effect infarcts, caused by capillary embolism. Their irregular distribution and variability in size in the spleen under consideration does not bear this out. Furthermore, the miliary lesions in the liver of this case, nontuberculous, can only be explained on the ground of local active infection.

In attempting to establish the real cause of such lesions we considered the possibility of a more or less indefinite protoplasmic form of the organism, possibly endowed with an ameboid motility, upon which the customary capsule would not, for a time, at least, develop. Such an organism might easily escape detection in lesions since the protoplasm of the blastomyces cannot be brought out differently by tissue stains, though the capsule can be differentially stained, particularly by Mallory's connective tissue stain. We have applied a considerable variety of stains to sections of the lesions described, but have obtained no definite results. In many of these sections the connective tissue stain reveals more or less homogeneous grayish to blue colloid bodies which cannot be distinguished from certain nonfuchsinophilic inclusion bodies occasionally found in other lesions. Although they may merely represent a result of cell degeneration, their unusual number in the spleen and liver lesions described make them of rather more than passing interest.

As for the treatment and prognosis of blastomycosis, nothing new can be added as a result of our experience. It still seems that the truly systemic infections are very refractory to treatment, and seldom recover. It is possible, however, that as a result of further experience this statement will be modified, as it is not unlikely that some strains of the organism will be found more amenable to treatment than others, a matter to be borne in mind. Potassium iodid in large doses is indicated, together with general dietary and hygienic measures. The localized surgical infections, on the other hand, are not infrequently curable by a combination of medication and surgical interference. A consideration of the cases in Table 1 seems to indicate, as in Case 25, for instance, that radical measures should not be too long delayed.

Vaccine therapy offers a field for further experimentation and observation. Stober cured one systemic case and concluded that the

method might be useful in diagnosis and valuable in therapeutics. Breed's results in this connection are also of interest. It must be noted, however, that systematic work, such as that with the blastomyces by Davis and with *Coccidioides immitis* by Cooke,³¹ has failed to indicate any high degree of immunologic reaction in such infections, which would make it appear doubtful whether constantly good results can be expected by attack along these lines. In but one of our cases, Case 4, was the organism recovered in pure culture in time to prepare a vaccine. The condition of the patient was then, however, too poor to warrant its use.

The five cases of systemic blastomycosis encountered in this department occurred within less than a year, between July, 1914, and January, 1915, inclusive. This, however, does not necessarily indicate the frequency of occurrence in this locality, since no case has been detected among the 450 necropsies performed since that time. The following reports are made as brief as is consistent with a clear exposition of the condition.

REPORT OF CASES

CASE 1.—H. J., colored, laboring man, aged 32, single, a native of Louisiana, was admitted to the Charity Hospital, Ward 34 (service of one of us), Jan. 22, 1914, complaining of pain in the right side of chest, cough, fever and expectoration.

His history was negative. Present illness began three months before with cough and pain in the right chest, the latter recently extending to the shoulder. For two months had expectorated purulent material. Had fever late in the day and sweats at night.

On physical examination the patient was found to be a well-developed and well-nourished man. The superficial glands were palpable. Inspection showed a marked diminution of expansion on right side of the chest, slight on the left. Tactile fremitus was diminished and dullness was marked on the right side, especially in the upper part. Here was a distinctly visible pulsation which was felt on palpation. Respiratory sounds here were practically absent; voice sounds were diminished. Over this area a distinct bruit was heard, synchronous with the second sound of the heart. Respiratory and voice sounds were diminished throughout, and friction sounds were present in the right axilla.

The heart was negative except for a slight increase to the right. The liver was palpable one and one-half inches below the costal arch. The abdomen was otherwise negative.

The temperature at admission was 101, respiration 28, pulse full, feeble and regular. The blood pressure was the same in both arms, systolic 110 and diastolic 50. The blood counts showed 10,000 white and 3,900,000 red cells. Hemoglobin was 60 per cent. (Tallqvist). The Wassermann reaction proved negative, original and Tschernogubow technics. Specific gravity of urine 1.030, hyaline and granular casts. Though the sputum was repeatedly negative, the provisional diagnosis was pulmonary tuberculosis, probably with aortic aneurism. The roentgenologist reported "probable thoracic tumor."

On March 16 a small, freely movable nodule had appeared above the right clavicle. This rapidly enlarged, became fluctuant and was incised on the third or fourth day, when a small quantity of thick, yellowish pus was evacuated. The skin lesion quickly healed. On March 20 another hard nodule was noticed

31. Cooke, J. V.: ARCH. INT. MED., 1915, xv, 497.

on the nose; it quickly softened, was opened and rapidly healed. The purulent material obtained was negative for *B. tuberculosis* and cultures were reported sterile.

About six weeks before death a large abscess appeared on the right leg below the knee. This rapidly attained a diameter of about eight inches when it was opened and about a pint of pus obtained. In two or three weeks the lesion was completely healed. This pus was also reported negative for bacteria, in smears and cultures.

The patient became emaciated and began to have severe paroxysms of coughing, with free expectoration of a mucopurulent material, frequently bloody. The physical signs were those of cavity formation. The clinical course was septic, the temperature remaining between 100 and 103. The heart became rapid and weak, respiration increased in frequency, and the cough, expectoration and sweats continued until the patient died, May 19, 1914.

In view of the fact that at no time had tubercle bacilli been found, the diagnosis of pulmonary tuberculosis, as given by the intern at the time of death, was believed to be incorrect.

Necropsy (A, 14, 175) was performed (W.) on May 22, 1914, seventy hours post mortem. The findings in abstract are as follows:

The body is fairly well developed but emaciated. No ulcer or subcutaneous abscess is evident, though there are small scars over the right clavicle, on the nose and below the right knee.

The peritoneal cavity shows very little fat. The mesenteric lymph nodes are enlarged. The pleural cavities are obliterated in their upper portions by firm adhesions, those on the right side being so firm as to necessitate cutting the lung from the chest wall. No free fluid or acute exudate is noted. In removing the right lung several abscesses are cut or torn into, some of which involve the chest wall. They contain a thick, semifluid material, yellowish gray in color and of a peculiar odor. On section numerous smaller cavities are found, separated by zones or walls of increased connective tissue. These walls are covered by necrotic material and purulent exudate. The lower lobe is large, heavy, dark red in color and contains numerous small, usually grayish areas of solidification. The larger show central necrosis. The left lung presents a condition essentially similar except that there is a greater amount of apparent organization with but a few small abscesses.

The organs of the neck are examined here because of apparent involvement in the condition found in the right pleural cavity. Below the thyroid and behind the upper part of the sternum and right clavicle is a small abscess. This does not communicate with the surface or directly with the cavity of the adjacent lung.

The spleen is enlarged and weighs 200 gm. On section there are found areas of an apparently granulomatous change, firmer and paler than the splenic pulp. The liver is large, pale and irregularly yellowish in color. On section numerous small grayish areas are seen, apparently of the same process as that involving the other organs. The pancreas, which is small and weighs but 60 gm., appears normal except for a small, yellowish abscess near the caudal end. This contains thick pus. The walls are firm and fibrous in consistence. The gastro-intestinal tract shows only a few small, indefinitely ulcerated areas in the lower part of the small intestine and in the colon. These are not distinctive in appearance. The left kidney weighs 200 gm., the right 185 gm. On section the parenchyma bulges. The cortex is somewhat thickened and granular, the glomeruli injected and prominent. Organs not mentioned are essentially negative.

Rush sections of the lung tissue, made at the time of necropsy and stained with methylene blue, showed lesions thought to be typical of pulmonary tuberculosis.

The anatomical diagnosis was as follows: Original pulmonary tuberculosis; miliary tuberculosis of spleen and liver (and intestine?); abscesses, cervical, pleural and pancreatic; congestion and edema of lungs; acute nephritis.

Bacteriologically, smears showed numerous gram-positive, non-acid-fast diphtheroidal bacilli in the purulent material from the neck, pancreas and lung. This organism was isolated and given the number D 15 in the diphtheroid series of Harris and Wade. No tubercle bacilli or actinomyces were found. (These smears, which were preserved, were later reexamined and all found to contain small numbers of shrunken blastomyces, none of which has been seen to show budding.)

Microscopically the essential features of the tissue removed at necropsy were as follows:

Certain sections of the lung showed areas of a granulomatous change typical of tuberculosis; lymphoid and plasma, epithelioid and giant cells and necrosis. There were also found, however, round, red staining bodies, each with a more or less wide, hyaline, unstained capsule. These were present within giant cells and lying free among other cells. In some areas they were numerous and in others difficult to find. Sections from the abscesses showed an extensive combination of granulomatous and suppurative reactions. There were areas of fibrosis adjoining others which, on the one hand, showed extensive epithelioid proliferation, and on the other hand in which polymorphonuclear infiltration was extensive and beyond which abscess formation was evident. In some of these sections the blastomyces were found with difficulty. There were also found vast numbers of short, thick diphtheroidal bacilli.

The spleen pulp was congested. Large areas of necrosis were prominent about which were zones of epithelioid and lymphoid and plasma cells, with quite numerous giant cells. Prolonged examination revealed very few typical sclerosed yeast cells, although numerous bodies were encountered which may represent degeneration forms of these. The appearance is, as a whole, very typical of tuberculosis, though no tubercle bacilli can be found in specially stained sections. In the liver passive congestion is notable. Numerous small areas are composed largely of lymphoid and plasma cells with more or less numerous epithelioid cells in the larger areas. As in the spleen, a few degenerated blastomyces were found on careful search. One section of pancreas studied showed the wall of the abscess noted. A number of typical blastomyces were here seen among the cells of the lesion. Sections of the intestine showed nothing worthy of note. The areas thought to be ulcers were apparently caused by postmortem change. A section of the adrenal showed, besides marked post-mortem change, two plugs or colony masses of bacteria. They were apparently of the diphtheroidal bacillus found elsewhere. There was no tissue reaction about these masses. The kidneys showed no increase of the connective tissue, but parenchymatous degeneration was marked. The lining epithelium was everywhere granular, swollen, fragmented, and at times vacuolated, as if by fluid. Small masses of bacteria were found, about which no tissue reaction is seen. No blastomyces were found on prolonged search. The heart showed little but a fairly extensive fat vacuolation of the muscle fibers.

The corrected anatomical diagnosis was as follows: Blastomycosis of lung, spleen, liver and pancreas; blastomycotic abscesses, cervical, pulmonary and pancreatic, with secondary diphtheroid invasion; fatty myocarditis; acute parenchymatous nephritis; congestion and edema of lungs.

CASE 2.—M. K., aged 18 years, single colored man, native of Louisiana, laborer, was admitted to the Charity Hospital, Ward 34 (service of one of us), July 4, 1914, complaining of cough, expectoration, weakness, diarrhea, fever and sweats.

His history was negative. His present illness began nine months ago with a suppurating focus in the right inguinal region and another over the sacrum. These had persisted. About six months ago he began to have pain in the chest and to expectorate freely. About this time diarrhea developed and there appeared a roughened discoloration of the skin. Diarrhea has persisted, the bowels moving several times daily. Blood was seen in the stools, but none in the sputum.

Physical examination showed the patient to be emaciated. The skin over the wrist, ankles, about the mouth and at the elbows was dry, rough and brownish-black in color. The backs of the hands were also roughened. A discharging sinus 5 mm. in diameter was found in the right inguinal region. The surrounding skin was much thickened and indurated. An area of ulceration was also present in the sacral region.

There was a diminution of expansion on both sides of the chest, dulness, bronchial respiration, increased voice sounds and many fine and coarse moist râles. In both axillary regions the respiratory and voice sounds were greatly diminished because of pleural thickening. The heart was normal and the abdomen apparently negative. The temperature was 99 F.

A blood examination on admission showed a total white cell count of 16,000 and the hemoglobin 60 per cent. (Tallqvist). The systolic blood pressure was 100. The urine showed albumin (amount not recorded) and hyaline and granular casts. On July 5 and again on the next day the sputum was found to contain tubercle bacilli.

The patient was transferred to the tuberculosis division. On July 20 he had a severe pulmonary hemorrhage. Cough persisted and became progressively worse, the sputum at times being blood streaked. Weakness was pronounced and diarrhea, sweats and chills were very troublesome. The temperature was never high, and was subnormal for the last two weeks of the patient's life, death occurring July 28, 1914.

A clinical diagnosis of pulmonary tuberculosis and pellagra was made.

Necropsy (A, 14, 274) was performed (H.) July 29, 1914, fourteen hours postmortem. The essential findings were as follows:

The body is fairly well developed but emaciated. The skin about the angles of the mouth, over the posterior surfaces of the hands and wrists and of the forearms for a distance of from 5 to 6 cm. at the ankles and over the inguinal regions is of a dark, brownish-black color, very dry, rough and scaling and in places somewhat indurated. In the right inguinal region are several small scars and a number of small ulcerated areas from 0.5 to 1 cm. in diameter. These lesions are irregular in outline, with undermined edges, and present a granulating base covered with a small amount of thick, yellowish exudate.

The peritoneal cavity contains little fat. The mesenteric lymph nodes are moderately enlarged and pinkish gray. The diaphragm is at the fifth rib on the right and the fifth interspace on the left. Both pleural cavities are practically obliterated by many dense fibrous adhesions. The heart weighs 190 gm. On section the musculature is brownish red, somewhat soft in consistency, but resistant to pressure. The valves are negative.

The lungs are removed with difficulty, a portion of the right upper lobe requiring to be cut away. Throughout both lungs many small areas of consolidation are felt; on section these are seen to be grayish yellow in color and surrounded by zones of connective tissue increase. Some of the larger of these show necrosis. In the upper lobe of the right lung are cavities which contain greenish yellow purulent exudate. The walls are made up of thickened connective tissue covered by necrotic material. The spleen weighs 80 gm. and shows nothing worthy of note. The liver is small and weighs 1,130 gm. Its outer surface is yellowish brown in color. On section some congestion is apparent. The vessels of the gastro-intestinal tract show some engorgement, while here and there minute petechial hemorrhages are seen. The right kidney weighs 190 gm. and the left 195 gm. On section the pulp bulges and the parenchyma is congested, the pyramids particularly so. The cortices seem diminished. The adrenals are negative, and the other organs present nothing worthy of particular note.

The anatomical diagnosis was as follows: Original pulmonary tuberculosis, pellagra; acute and chronic nephritis; chronic splenitis; passive congestion of the liver; chronic fibrous pleurisy, bilateral.

Microscopically, the observations worthy of note in this connection are as follows:

Sections of lung showed lesions with little acute infiltration but much necrosis. This seemed to be a mass, coagulation necrosis, since the outlines of the degenerated cells were frequently retained. There often seemed to be a preceding deposit of fibrin in the neighboring air sacs. About some of these lesions there was much fixed-tissue proliferation, with an infiltration of lymphoid and plasma cells, the latter being the more numerous. In other sections these smaller lesions had progressed to cavitation with secondary invasion and suppuration. In a few areas typical blastomycetes were found. These were within giant cells, endothelial phagocytes or were lying free in exudate or rarely in an uninvolved air sac. The number could not account for the extent of the lesions present. In many of these lesions, however, acid-fast bacilli could be demonstrated. There was an acute fibrinous exudate on the pleural surfaces.

The spleen showed little worthy of note. By careful search of several sections a very few partially degenerated blastomycetes were found, lying in sinuses with no evidence of local tissue reaction. The heart showed only a moderate hypertrophy. The liver showed no evidence of invasion by the blastomycetes. The atrophy of chronic passive congestion was quite marked. Sections of the kidneys showed congestion and hydropic degeneration of the parenchyma, but no evidence of blastomycosis. The other deep organs were practically negative.

In the sections of the only piece of skin which was preserved at necropsy, taken from the right inguinal region, there was found a condition which was made the subject of careful study. There was a lack of the epithelial proliferation and down growth common in cutaneous blastomycosis, but many small foci of necrosis were seen in the subcutaneous tissues. These were made up of large numbers of more or less degenerated endothelial leukocytes, of the débris from many very large giant cells of peculiar appearance, and of vast numbers of blastomycetes. Most of these parasites were so small as to be recognized with difficulty. Many could be made out definitely only by oil-lens study of specially stained sections, in which the very delicate, blue-staining capsular membranes were brought out. Budding was very active and occurs even in the smallest organisms, thus explaining the great number of minute cellules found.

The corrected anatomic diagnosis was as follows: Pulmonary tuberculosis; blastomycosis of the lungs and skin; pellagra (?); acute parenchymatous nephritis; hydropic; passive congestion of liver; chronic splenitis; hypertrophy of the heart; chronic fibrinous pleurisy, bilateral.

CASE 3.—J. T., a colored laboring man, aged 36 years, native of Louisiana, was admitted to the Charity Hospital, Ward 23, July 31, 1914, complaining of abscesses on the chest wall and ankle, cough, fever and sweats.

His history was negative. Present illness began about four months before admission, when he developed a "cold" with cough and fever. A number of abscesses appeared, especially on the chest.

Examination showed that the patient had lost flesh. On his chest were five abscesses, three on the right side and two on the left. These varied in size from a marble to a pigeon's egg, were very painful and fluctuated. Examination of the chest revealed many areas of slight dulness, numerous râles, fine and coarse, dry and moist. The respiratory and voice sounds were increased. The heart and vessels showed nothing abnormal. Temperature was 100, pulse 112 and respiration 32.

Blood examination revealed 12,000 white cells, and Wassermann reaction negative by both original and Tschernogubow technics. The urine showed 1 per cent. albumin and hyaline and granular casts.

Abscesses continued to appear over various regions, namely, over the heart, left eyebrow, left side of neck and jaw. The patient continued to grow worse, with progressive emaciation, cough, free expectoration of a mucopurulent material, fever and sweats. The urine averaged 32 ounces in twenty-four

hours. The temperature seldom went above 100 and never above 101 until just before death, which occurred Oct. 16, 1914.

The clinical diagnosis was pulmonary tuberculosis, multiple tuberculous lymphadenitis, tuberculosis of the skin.

Necropsy (A, 14, 352) was performed (H.) Oct. 17, 1914, twenty-four hours post mortem. In abstract the findings were as follows:

The body is fairly well developed but emaciated. Three cutaneous ulcers are found. One, 1.5 by 3 cm., is above the left eyebrow; the second, of about the same size, is below the ramus of the left jaw; the third, 4 by 6 cm., is on the left side of the chest over the costosternal articulation of the fourth and fifth ribs. These ulcerations extend to the musculature. The edges are indurated, undermined, bluish gray in color and the floors are covered with thick, yellowish exudate. Five subcutaneous abscesses are present on the chest, three on the left and two on the right side. These average 4 cm. in diameter and contain a thick, purulent material. The peritoneal cavity is practically negative. The diaphragm is at the fifth interspace on the right and at the sixth rib on the left. The mesenteric lymph nodes are enlarged and average 1.5 cm. in the greatest diameter. They are dark, grayish yellow in color and many show areas of necrosis. The pleural cavities show many dense, fibrous adhesions to the apex and upper lobe of the lungs, and contain 150 to 200 c. cm. of a dark, amber-colored fluid. The heart is slightly increased in size, owing to the dilatation of the right side, and it weighs 265 gm. The valves and other structures are negative. Many hard nodules are felt throughout both lungs, most numerous in the apices. These vary in size from small, shotlike areas to masses 1.5 cm. in diameter. On section they are grayish yellow in color and surrounded by a zone of congestion. The larger show central necrosis. Two small cavities are present in the right apex. The peribronchial lymph nodes are slightly enlarged and show some necrosis. The spleen weighs 110 gm. and presents nothing of importance. The liver weighs 1,570 gm. On section some engorgement of the venous channels is seen, otherwise the organ is negative. The right kidney weighs 135 gm. and the left 130 gm. Both are congested and show evidence of a considerable connective tissue increase. In the cortical portion of the right kidney, near the upper pole, are six small, yellowish-gray, nodular areas, each measuring approximately 2 mm. in diameter. These are outlined by congestion zones. The organs not discussed show nothing worthy of particular note.

The anatomical diagnosis was as follows: Original pulmonary tuberculosis; tuberculosis of kidneys; tuberculous lymphadenitis, mesenteric and bronchial; lupus vulgaris, face and chest wall; dilatation of heart; chronic pleuritis with effusion; chronic splenitis; chronic nephritis; passive congestion of the liver.

The microscopic examination showed the following features:

Sections of the lung were studded with miliary areas. Many of these were found to be largely collections of polymorphonuclear leukocytes, at times with much fibrin deposit, containing relatively few proliferated cells. They all contained greater or smaller numbers of the sclerotic cells of the blastomyces of various shapes, many of which were in giant cells. Other areas were largely or entirely proliferative. The larger of these showed central necrosis and suppuration. The blood spaces throughout were engorged and many desquamated pigment-bearing cells were seen. In areas of the spleen diffuse, partial degeneration was seen, being apparently postmortem changes. Throughout were many somewhat diffuse collections of polymorphonuclears. Many bacteria were present, in masses and diffusely scattered. No lesions of blastomycosis were found. In the liver were numerous collections of a few polymorphonuclears and scattered here and there were small, tuberclelike lesions showing, besides the infiltration, a fixed-tissue proliferation. A few of these showed small groups of blastomycetes, some within giant cells. The majority showed no distinct parasites, although peculiar, somewhat hyaline bodies, possibly unrecognized forms of these, were encountered. Here and there were collections or masses of irregular, hematoxylin-staining bacilli. In the adrenal were several postmor-

tem colonies of such bacteria. In certain sections of the kidney tissue blastomycotic lesions were found, in which a minimal amount of proliferative reaction, but much suppuration, was evident. The organisms were sometimes found free in blood spaces or in kidney tubules, without local tissue reaction. There was nothing else noteworthy except a moderate connective tissue increase. The skin lesions were quite typical of cutaneous blastomycosis. There was noted here and there an organism, usually with no local leukocytic infiltration, lying within the epidermis. Another feature was the unusual number of bizarre hyaline accumulation bodies which had developed by deposit increase of the capsules or shells of dead blastomycetes.

The corrected anatomical diagnosis was systemic blastomycosis, involving skin, lungs, liver, kidneys and lymph nodes; acute plastic and chronic fibrous pleuritis; dilatation of heart; chronic passive congestion of lungs and liver; acute infiltrative and chronic proliferative splenitis.

CASE 4.—R. B., a single white man, aged 30 years, a native of Louisiana, was admitted to the Charity Hospital, Ward 68, Aug. 29, 1912, for treatment of growths ("papillomata") on hand and foot.

The history showed that his mother and sister died of pulmonary tuberculosis, but was otherwise negative. His present illness began about three months before admission, when fingers, hands and toes became painful. After several weeks an abscess appeared on one hand and this was opened. A week later another developed on the foot. Several weeks before admission an abscess of the back was opened and pus liberated. About two months ago there appeared on the lip, back of hand and on the great toe, cauliflower growths, which have enlarged, but have not suppurated.

Aside from these, the physical examination at admission was practically negative. Patient was in fairly good condition, seemed to be feeling well, and had no pain, cough or fever. Large doses of mixed antisiphilic treatment were given for a long time. On August 30 pus was found in the urine but no albumin. The source of the pus is not recorded. On September 5 the Wassermann reaction was negative. The patient was discharged Oct. 8, 1912, showing much improvement.

After several months the patient applied, June 14, 1913, to the Louisiana Antituberculosis League for treatment. There he was examined by one of us (B.). The symptoms were subnormal temperature in the morning, rising to 99 and 99.8 F. late in the day; slight cough; expectoration in the morning; pain in the left side of the chest; "dyspepsia"; loss of weight. Examination showed lagging on the left side, diminished tactile fremitus, slight dullness, diminished respiratory and voice sounds and in places fine, moist râles. A diagnosis of tuberculosis of the upper part of the left lung and tuberculous pleurisy was made. The patient was sent to a tuberculosis camp, where he remained for four months with but moderate benefit. An abscess of the back having developed, he was advised to return to the hospital for treatment.

The patient, then aged 32, was readmitted Oct. 17, 1913, to Ward 68. Examination showed two large abscesses of the back, on the right side, thought to be tuberculous, with necrosis of several of the adjacent ribs. There was evidence of pleural and probably of pulmonary involvement.

Pus from the lesions contained bacteria identified culturally as pneumococci, but no tubercle bacilli were found. Wassermann reaction on October 18 was negative by the original and Tschernogubow technics. Mixed treatment was nevertheless ordered and continued for four months, with apparently little benefit.

October 22 resection of parts of two ribs, with thorough local curettage, was performed. On November 12 a portion of another rib was resected. On Jan. 7, 1914, the upper half of the former operation wound had healed, leaving a large sinus in the lower half leading obliquely upward to the ends of the previously resected ribs. Several of these ends were found exposed and necrotic. Under ether the old incision was opened, masses of soft granulation tissue removed

and a number of pockets curetted. Pleural involvement appeared on the next day, the patient being unable to breathe without severe pain. Sputum on January 9 still showed no tubercle bacilli. A consultant on this date reported the lungs negative so far as physical examination was then practicable.

On March 9, without anesthetic, the cavity and sinuses were injected with Beck's paste preparatory to Roentgen-ray examination. The roentgenologist reported "vertebrae negative, small masses of bismuth scattered through lung on right side, also a small amount in left side near base." On April 15 the wound was again curetted and more necrotic bone removed.

On two occasions the same dermatologist diagnosed the skin lesion of the face as "late tubercular syphilide." On Sept. 29, 1914, tissue curetted from the chest wall was first sent to the laboratory. In the sections blastomycetes were recognized. Cultures after two weeks gave white, fluffy growths. *Bacillus tuberculosis* was never found.

In November an abscess of the thigh was opened and early in December another posterior to the right knee was incised. Pulmonary involvement was now extensive. Many organisms were found in the sputum, and cough was severe and expectoration abundant. On December 11 the total white cell count was 13,700, neutrophils 74, lymphocytes 19, endothelial leukocytes 4, and eosinophils 2 per cent. Late in December the lesion of the back reached the cord, producing a myelitis. The constitutional symptoms were characteristic. The loss of weight and weakness were extreme. The pulse and respiration were both rapid and weak, and chills and sweats were very annoying, though in the last few weeks the temperature was persistently quite low. Death occurred Feb. 3, 1915.

The corrected clinical diagnosis was systemic blastomycosis involving the lungs, ribs, vertebrae, cord, back, face, thigh and knee, with secondary invasion of lesions by a nonpathogenic streptococcus.

Postmortem examination was not permitted.

CASE 5.—M. N., a German, aged 61 years, was admitted to the Charity Hospital, May 14, 1914, complaining of cough, pain in chest, shortness of breath and weakness.

His history revealed that he had had pneumonia many years ago, but otherwise he has always been well. His present illness began with a slight cold early in February and since then he has had a cough, increasing in severity. He had expectorated but little and this never blood streaked. He has lost no weight. Examination showed the patient to be well developed and fairly well nourished, apparently not very sick. Slight edema of legs was noted. The heart was slightly enlarged to the right and downward. A faint systolic murmur was noted, heard best at the apex. The pulse was somewhat fast and slightly irregular. The arteries were markedly sclerotic. Percussion gave dullness over the upper lobes of the lungs. Râles were heard everywhere, most marked in the upper lobes. The abdomen was negative. The sputum was negative for tubercle bacilli. Probable diagnosis was pulmonary tuberculosis.

The patient was transferred on May 25 to a medical service, Ward 16, on account of bronchial asthma and valvular heart disease. The sputum was still negative. The urine was practically negative. The Wassermann reaction was weakly positive by the original technic and strongly positive by the Tschernogobow reaction. Blood pressure was 100 diastolic and 180 systolic. The von Pirquet tuberculin reaction was negative. Antisyphilitic treatment was not beneficial. Dyspnea increased in severity and frequency of attacks. The material expectorated was sometimes blood tinged.

Early in July sore areas were noticed in the scalp, and a small ulcer appeared on the left side of the face. The nodule under the scalp became semifluctuating. These lesions increasing, patient was transferred on July 6 to a surgical service, Ward 66, with a diagnosis of carcinoma of face and abscess of scalp. Histologic examination of tissue from the face lesion showed the condition to be very typical cutaneous blastomycosis. The bones of the skull were

found eroded on July 13, and a second abscess of the scalp soon appeared. The temperature had fluctuated between normal and 101 since admission, but on July 29 it rose to 104. The leukocyte count at this time was 24,000, with 87 per cent. polymorphonuclears. The right arm soon became painful at the elbow. On August 10 an abscess was opened and erosion of all the articular surfaces of the elbow noted. The scalp was reopened at the same time and the bone curetted. In August the patient left the hospital against advice.

On November 11 he was readmitted to Ward 71. He had lost 15 pounds in weight and was very weak. He coughed a great deal and had abundant blood-streaked sputum. The elbow sinus was still discharging.

All lesions progressed. Late in December two new abscesses appeared on the chest wall. The elbow infection extended through the forearm. The general condition continued to grow worse, the patient became septic and died Jan. 18, 1915.

The clinical diagnosis was blastomycosis.

Necropsy (A-15-25) was performed (H.) Jan. 20, 1915, forty hours post mortem. The essential findings were as follows:

The body is fairly well developed but emaciated. The lower extremities and right arm are edematous. The superficial lymph nodes are enlarged. On the left cheek is an indurated ulcer 5 cm. in diameter, having a granulating base showing yellowish, purulent exudate. There is a similar area, 2 by 4 cm. on the skin. Two abscesses are found beneath the scalp and two on the chest, one over the third right and the other over the fifth left costosternal juncture. The scalp abscesses communicate with intracranial collections of pus, while those on the chest arise from necrotic ribs. From the lower abscess a sinus continues inward through the fifth intercostal space and leads into the pericardial cavity. Discharging sinuses are present at the elbow of the right arm, where the bones are eroded, and extend by tracts between the muscles of the forearm to the hand. Here are sinuses and considerable necrosis of the bones of the wrist.

The peritoneal cavity is negative. The diaphragm is at the sixth rib on the right side and the sixth interspace on the left.

On raising the sternum a large collection of pus is encountered, which communicates externally with the lower subcutaneous abscess and internally with the pericardial cavity. This shows dense fibrous adhesions, among which are numerous pus foci. The heart is removed with difficulty on this account. The condition of this organ is so remarkable that it has been made the basis of a special communication. Briefly, it is much larger than normal and weighs 420 gm. Its surface shows several irregular, grayish-yellow necrotic areas which extend deep into the myocardium. One lesion in the wall of the right auricle extends through the muscularis and involves the endocardium. On opening the right auricle many minute grayish white nodules are seen on the inner wall. Some of these are entirely subendocardial, while others protrude into the cavity from 1 to 2 mm. Some of these show central cavities, and thus present the appearance of minute craters. The interauricular septum is pushed well into the right cavity by a large lesion in this wall. This protrusion is less marked in the left auricle. The muscularis of the left ventricle is much thickened, averaging 2.2 cm. The endocardium of this chamber is negative. The valves present nothing worthy of note.

The right pleural cavity contains 1,000 c.c. of clear amber fluid. There are many shreds of fibrin on the surfaces. Dense adhesions are also present at the apex and posteriorly. The left cavity contains 150 c.c. of fluid, and many firm adhesions. On pressure many shotlike nodules are felt throughout both lungs. Other larger areas of consolidation are noted. On section there are seen many grayish-yellow, solid areas surrounded by zones of connective tissue increase. Between these the lung tissue is red, and heavy and frothy red fluid exudes on pressure. The largest of the solid areas show necrotic centers. Three small cavities are found in the middle lobe of the right lung. The peribronchial lymph nodes are moderately enlarged.

The spleen weighs 280 gm. It is large and in the abundant, deep-red pulp are seen several small, soft, grayish-white nodules, pinhead in size and indistinctly marked off from the surrounding tissue by congestion. The liver weighs 1,480 gm. On section marked venous congestion and a slight connective tissue increase is apparent. The combined weight of the kidneys is 285 gm. Both show a diminution of the cortical substance and moderate congestion. The organs not mentioned present nothing worthy of note. The skull shows two irregular perforations at points corresponding to the scalp lesions. The smaller anterior perforation is continuous with a small epidural collection of pus. The dura here is much thickened and very adherent to the calvarium. Beneath the posterior opening the dura has been penetrated and the suppurative process has invaded the left cerebral cortex. The brain weighs 1,450 gm. The dura is adherent to it at both points of skull perforation. At the posterior lesion the cortex has been invaded to a depth of 0.7 cm. by the process and shows some necrosis. This is at the left superior parietal gyrus.

The anatomical diagnosis (original) was blastomycosis of the skin, lungs, bone, brain, spleen, pericardium and heart; acute and chronic splenitis; acute and chronic nephritis; chronic pleurisy with effusion.

Bacteriological examination showed blastomycetes in the preparations from the fresh material from the subcutaneous abscesses, the lungs and the pericardium, which were recovered culturally.

Sections of the heart showed, beside marked hypertrophy, areas of extensive blastomycotic invasion. The deeper, invading parts of the lesions appeared as small, discrete tubercles which showed an affinity for the connective tissue strata. Toward the pericardial surface, where the lesions were older, these had undergone fusion and showed much necrosis, with strands of connective tissue increase. Large numbers of blastomycetes were found in all sections and many of these were undergoing budding. There were also found in a few places peculiar homogeneous, hyaline bodies, similar to those described in another case in this series. The lung sections were studded with typical miliary blastomycotic lesions. The organisms were found in all lesions, but not in great numbers. The spleen showed little but a marked congestion and a fairly widespread polymorphonuclear leukocytic invasion, quite marked in places. There could be found no evidence of blastomycotic invasion. The liver showed much passive congestion, with here and there a miliary lesion of blastomycosis. In but a few of these, however, could the typical blastomycetoid bodies be found. The kidney sections showed a fairly marked congestion and considerable irregular connective tissue increase. The parenchyma was swollen in places and showed much granular degeneration. The brain showed the meninges and the underlying cortical tissue to be involved in the process which caused the bone erosion. Here was much infiltration and necrosis and little or no proliferation reaction. No giant cells were seen within the cerebral substance, though several were present in the meningeal lesion. Sections of bone showed necrosis, leukocytic infiltration and proliferation of the fixed tissue. Numerous giant cells were seen, the most of which contained blastomycetes. The lesions of the skin and subcutaneous tissues were very typical of blastomycotic infection.

The corrected anatomical diagnosis is as follows: Systemic blastomycosis, involving lungs, pericardium and heart, liver, brain and ribs and bones of skull; blastomycosis of skin of face, with abscesses of scalp and chest wall; acute splenitis; acute parenchymatous and chronic interstitial nephritis; acute plastic and chronic fibrous pleurisy, with effusion.

It may be noted that in certain of the foregoing reports the clinical records are not as complete as is desirable. This is at times unavoidable in the overcrowded colored wards of a charity hospital, particularly when so commonplace a condition as tuberculosis is under treatment.

Several features have been noted which were unusual to generalized blastomycosis from the pathologic point of view or have been thought otherwise worthy of special note. Briefly, these are, in Case 1, the extensive lesions of the spleen and liver, apparently due to the blastomyces, in which very few yeast cells could be found. In Case 2 there was an apparent secondary invasion by the blastomyces of a pellagrin suffering from pulmonary tuberculosis. In the skin lesion very interesting minute forms were found and specially studied. In Case 5 the heart was very extensively involved, the condition being apparently unique. Widespread secondary bacterial invasion has been noted. These features have been considered in more or less detail.

In conclusion it may be said that nonrecognition of the blastomycosis still presents a minor problem in medical education, and the occurrence and clinical and pathologic features of the disease should be more generally understood. As has often been said, the usual error is to regard it as tuberculosis. It needs no argument to show the desirability of promptly recognizing these infections, not only from the viewpoint of mere accuracy of diagnosis and vital statistics, but from that of proper treatment, of prognosis and of prophylaxis. That blastomycosis may occur more frequently than has been recognized may be indicated by the present report of five cases discovered in fairly rapid succession in a community from which, so far as available records indicate, only the cutaneous type of infection had previously been reported. The necessity for use of the microscope in the establishment of the correct diagnosis cannot be too strongly emphasized.

We wish to express our thanks to Dr. C. W. Duval for suggestions, and particularly to Dr. T. D. Hurley of Kansas City, Mo., who as senior pathologic intern necropsied three of our cases, and studied the conditions with us. His removal from the city prevented his more active collaboration in the present article.

METABOLISM STUDIES BEFORE AND AFTER SPLENECTOMY IN A CASE OF PERNICIOUS ANEMIA *

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The present case is reported as a corollary to the other studies of metabolism before and after splenectomy reported from this laboratory.¹

In one of these² the literature concerning metabolism in anemia, before and after splenectomy, is thoroughly reviewed. Few references to the literature therefore will be given here. In brief the results of studies of metabolism before and after splenectomy for various types of anemia and in normal animals may be summarized as follows: (1) There is little or no change in the total nitrogen metabolism or in its partition, with the exception of a decrease in the uric acid excretion after splenectomy in certain cases. (2) A decrease in the elimination of iron occurs in certain cases after splenectomy. (3) A decrease in the output of urobilin and urobilinogen is noted in certain cases after splenectomy.

This decrease in the daily elimination of uric acid, iron and urobilin after splenectomy is apparently most marked in those cases in which before splenectomy there has been conspicuous evidence of increased hemolysis, indicated by abnormally high excretion of uric acid, iron and urobilin or by a lemon yellow color of the skin.

Robertson³ emphasizes the fact that cases which had shown a high urobilin excretion before splenectomy and in which after splenectomy the urobilin output exhibited only a transient reduction, or none at all, did not show as much improvement in other respects following the

* Submitted for publication April 24, 1916.

* From the John Herr Musser Department of Research Medicine and the Medical Division of the University Hospital, University of Pennsylvania.

1. Austin, J. H., and Pearce, R. M.: The Influence of the Spleen on Iron Metabolism, *Jour. Exper. Med.*, 1914, xx, 122. Goldschmidt, S., Pepper, O. H. P., and Pearce, R. M.: Metabolism Studies Before and After Splenectomy in Congenital Hemolytic Icterus, *THE ARCHIVES INT. MED.*, 1915, xvi, 437. Goldschmidt, S., and Pearce, R. M.: Studies of Metabolism in the Dog Before and After Removal of the Spleen, *Jour. Exper. Med.*, 1915, xxii, 319.

2. See paper by S. Goldschmidt, O. H. P. Pepper, and R. M. Pearce, reference given in Footnote 1.

3. Robertson, O. H.: Urobilin in the Stool in Pernicious Anemia, as Influenced by Splenectomy, Transfusion and Salvarsan, *THE ARCHIVES INT. MED.*, 1915, xvi, 429.

operation as did those cases in which the urobilin output was permanently reduced after splenectomy. However, Lee, Vincent and Robertson⁴ state that in some cases of severe anemia which showed marked symptomatic improvement for several months after splenectomy there was throughout this postoperative period a continued high excretion of urobilin. The highest degrees of hemolysis over a prolonged period are probably to be found in congenital hemolytic icterus. In the study of this condition reported from this laboratory² the output of uric acid showed a decrease of 47 per cent. after operation, the iron in the feces decreased 40 per cent. and the excretion of urobilin plus urobilinogen after the splenectomy was only about one-ninth that before the operation. The excretion of these substances had been extremely high before the operation.

The case here reported was studied in contrast as a case of pernicious anemia with evidence of increased hemolysis. The study was limited to the total nitrogen, the uric acid, the iron and the urobilin and urobilinogen. Three periods were studied: one before transfusion and splenectomy, one two weeks after splenectomy, and the third two weeks later. During each period the patient was on a carefully controlled Folin metabolic diet, and the period was not commenced until the patient had reached an approximate nitrogen balance. The nitrogen of the food and urine was determined by the Kjeldahl-Gunning method, the uric acid according to Folin's permanganate method, the iron by Neumann's method and the urobilin and urobilinogen according to the method of Wilbur and Addis. Only negligible amounts of urobilin or urobilinogen were at any time found in the urine.

The history and findings in the case will be given briefly. The blood examinations are tabulated in Table 1 and the metabolic results in Table 2.

Clinical Notes.—The patient, a man, aged 40, had complained for two years of weakness, dizziness, dyspnea and edema. These symptoms were steadily becoming worse. In other respects his history is unimportant. The physical examination revealed nothing noteworthy other than the signs of intense anemia, associated with a lemon yellow pallor. The liver edge was just palpable. At operation the spleen was found to be about three times its normal size, weighing 340 gm. The pathologic examination of the spleen showed chronic diffuse and follicular hyperplastic splenitis, with passive congestion and excessive pigmentation. The Wassermann was negative. On account of a constant eosinophilia repeated careful examinations were made of the stools for ova or parasites, but with negative results. The other laboratory reports are unimportant. The patient improved gradually after the splenectomy and six months later was doing fairly arduous work, apparently in perfect health.

4. Lee, R. I., Vincent, B., and Robertson, O. H.: Immediate Results of Splenectomy in Pernicious Anemia, Jour. Am. Med. Assn., 1915, lxx, 216.

TABLE 1.—BLOOD EXAMINATIONS

Date	Hemo- globin, %	Erythro- cytes	Leuko- cytes*	Nucleated Erythrocytes	Reticu- lated Erythro- cytes, %	Remarks
3/28/15	26	1,150,000	4,600	Normoblasts + Megaloblasts +	Coagulation time, 4.5 min.
4/ 8/15	25	1,620,000	5,800	Megaloblasts +		
4/15/16	20	1,110,000	2,000	0	4	Hemolysis in NaCl: partial 0.425, com- plete 0.325
5/ 3/15	20	1,700,000	6,500	0	2	Left hospital for a month
6/ 5/15	28	1,300,000	4,300	Normoblasts +	1	Platelets less than 100,000
6/ 7/15	Transfusion 900 c.c.
6/ 8/15	40	1,810,000	3,800	0		
6/12/15	Spleneectomy
6/15/15	37	1,420,000	16,600			
6/21/15	40	2,930,000	12,000	Normoblasts ++		
6/24/15	Severe hemorrhage from throat
6/24/15	27	After the hemorrhage
6/28/15	28	1,640,000	3,700	Normoblasts +		
7/ 9/15	31	1,630,000	6,300	0		
7/15/15	35	2,370,000	6,000	Normoblasts + Megaloblasts +		
7/22/15	48	2,030,000	8,100	Normoblasts +		
7/30/15	55	2,570,000	7,400	Normablasts +		
8/ 6/15	69	2,300,000	9,100	Normoblasts +	1	Howell-Jolly bodies +
8/16/15	48	3,200,000	8,300	0		
8/24/15	54	3,700,000	8,400	0		
8/29/15	70	3,580,000	9,400	0		
8/30/15	Discharged
1/ 8/16	83	4,400,000	10,500	Normoblast, occasional	Count by Dr. S. L. Freeman

* The differential counts of the leukocytes always showed a slight eosinophilia, but were otherwise normal. The erythrocytes showed the changes characteristic of severe anemia; these became less marked as the anemia disappeared.

TABLE 2.—EFFECT OF SPLENECTOMY ON ELIMINATION OF URIC ACID, IRON AND UROBLIN

Period	Date	Weight in Pounds	Nitrogen Intake, Gm.	Urine			Feces		Total Nitrogen Output, Gm.	Nitrogen Balance, Gm.	Uroblin and Urobilinogen
				Amount, G.c.	Total N, Gm.	Uric Acid, Mg.	Total N, Gm.	Iron, Mg.			
I	4/28/15	170½	16.7	1,550	14.8	762	1.46	17	16.26	+0.44	4/9/15 to 4/12/15, 18,300 per day
	4/29/15	17.6	1,820	16.2	824	1.46	17	17.66	-0.06	
	4/30/15	16.7	1,600	13.7	728	1.46	17	15.16	+1.54	
	5/ 1/15	17.2	1,680	14.5	788	1.46	17	15.96	+1.24	
	5/ 2/15	172½	16.6	2,200	16.2	852	1.46	17	17.66	-1.06	
	Average	16.96	1,770	15.08	791	1.46	17	16.54	+0.42	
	6/12/15	175	Spleneetomy								
II	6/24/15	15.7	1,160	10.86	500	1.09	10	11.95	+3.75	6/25/15, 16,500 per day 6/28/15 to 7/2/15, 16,000 per day
	6/25/15	16.8	1,340	12.43	520	1.09	10	13.57	+3.23	
	6/26/15	17	1,600	14.76	740	1.09	10	15.85	+1.15	
	6/27/15	17.3	1,590	15.54	680	1.09	10	16.63	+0.67	
	Average	16.7	1,420	13.41	610	1.09	10	14.50	+2.20	
III	7/ 6/15	160½	17.2	1,600	14.2	680	1.97	..	16.17	+1.03	
	7/ 7/15	16.3	1,380	14.1	680	1.97	..	16.07	+0.23	
	7/ 8/15	16.6	1.97	
	7/ 9/15	17.2	1,210	13.44	500	1.97	..	15.41	+1.79	
	7/10/15	16.8	1,310	15.06	620	1.97	..	17.03	-0.23	
	7/11/15	162	16.4	1,290	14.82	640	1.97	..	16.79	-0.39	
	Average	16.75	1,360	14.32	624	1.97	..	16.29	+0.46	
	8/22/15	190	8/18/15 to 8/22/15, 2,300 per day

COMMENT

The figures of this study as given in the Tables show that but little change in the elimination of uric acid and iron took place as a result of the splenectomy. The direction of the changes is, however, in each instance, in accord with the more pronounced changes reported where the hemolytic factor was more marked.

In view of the fact that the nitrogen balance is practically identical in the first and third periods, it may be concluded that splenectomy in this case, as in other cases reported in the literature, is without effect on the total nitrogen balance. The distinct positive balance during the second period is of interest, but probably of no significance in relation to splenic function. The uric acid elimination before operation can not be said to be other than a high normal figure, and the lower postoperative figures are still within normal range; but when it is considered that the diet and régime in general was identical before and after operation, the lowered output after operation is definite and significant. The same can be said of the figures for the iron elimination.

In the combined urobilin and urobilinogen elimination a definite change is noted following the splenectomy. Two weeks after splenectomy the diminution in the urobilin output was negligible, the difference between 18,300 units per day and 16,000 being too slight to permit of significance being attached to it. Two months after splenectomy, however, at a time when the blood count showed a pronounced and most satisfactory improvement, the urobilin output had fallen to one seventh of its former figure and had reached a low normal elimination.

SUMMARY

In an adult with pernicious anemia of a moderately hemolytic type, splenectomy was followed by disappearance of the discoloration of the skin and by prompt and persistent improvement in the condition of the blood and general health. Metabolism studies before and after splenectomy gave the following results.

1. A slight positive nitrogen balance before splenectomy was followed by an increased nitrogen retention fourteen days after operation and a return to the preoperative balance after one month.

2. The output of uric acid, although never exceeding normal limits, showed a decrease of 22 per cent. after operation.

3. The output of iron through the feces, although never above normal, showed a decrease of 40 per cent. after operation.

4. The excretion of urobilinogen and urobilin in the feces before splenectomy was about three times the normal; two months after operation the output was about one seventh of that before splenectomy.

BOOK REVIEW

MODERN MEDICINE. ITS THEORY AND PRACTICE. IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS. Edited by SIR WILLIAM OSLER, BART., M.D., F.R.S., Regius Professor of Medicine in Oxford University, England; formerly Professor of Medicine in Johns Hopkins University, Baltimore; in the University of Pennsylvania, Philadelphia, and in McGill University, Montreal; and THOMAS MCCRAE, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia; Fellow of the Royal College of Physicians, London; formerly Associate Professor of Medicine in Johns Hopkins University, Baltimore. In five octavo volumes of about 1,000 pages each. Volume IV. Diseases of the Circulatory System; Diseases of the Blood; Diseases of the Lymphatic System; Diseases of the Ductless Glands; Vasomotor and Trophic Disorders. *Just ready.* Price per volume, cloth, \$5, net; half morocco, \$7, net. Lea & Febiger, Publishers, Philadelphia and New York, 1915.

Volume 4 of Osler and McCrae's *Modern Medicine* deals with the diseases of the circulatory system, of the blood, of the lymphatic system and spleen, of the ductless glands, and with vasomotor and trophic disorders. It covers what is included in Volume 4, and in part of Volume 6 of the first edition. The general changes in typography, etc., have already been mentioned in the review of the first two volumes of the new System, in Volume XIV, page 608, of this journal.

Most of the chapters have been shortened to some extent, chiefly by the omission of the historical paragraphs, by the omission of discussions of the older theories as to the etiology and pathogenesis of various diseases, which as a result of recent advances in knowledge are now of historical interest only, and frequently by the omission or abbreviation of illustrative case reports. Many minor changes have been made, but in their general plan the articles are essentially the same as in the first edition.

A notable addition is an excellent chapter by Lewis on the Rate and Mechanism of the Heart Beat. The article by Abbot on Congenital Heart Disease has been enlarged and rewritten. The various subjects have been revised and brought up to date. This is especially true of the sections dealing with hemophilia and purpura; with the physiology and pathology of the adrenals, pituitary, and thyroid; with tetany; with the pathology of Hodgkin's disease, and with splenic anemia. Among minor additions may be mentioned short sections on *Streptococcus viridans*, endocarditis, on thrombo-angitis obliterans, on Gaucher's splenomegaly, and on hypopituitarism.

The new edition has lost nothing essential in the revision, and is an improvement over the old in its greater conciseness and compactness, as well as in its lessened cost.

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DIETARY DEFICIENCY AS THE ETIOLOGICAL FACTOR IN PELLAGRA *

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Having expressed the view that pellagra might, like beriberi and scurvy, be caused by a dietary deficiency¹ the writer was invited by the Robert M. Thompson Pellagra Commission to visit them at Spartanburg, S. C., for the purpose of investigating this phase of pellagra. Permission to accept this invitation was granted by the War Department, and the invitation was accordingly accepted. During my short stay at Spartanburg the pellagra commission has put all of their very numerous records and observations at my disposal, has made it possible for me to see a very considerable number of cases of pellagra, and has in every way possible endeavored to facilitate and expedite the investigation. In so far as these observations have any value at all, credit therefor should be awarded to the Robert M. Thompson Pellagra Commission, which has rendered the investigation possible. I also desire to express my indebtedness to several physicians of Spartanburg, but particularly to Dr. O. W. Leonard and Dr. J. H. Allen, who have kindly taken me to see a number of cases of pellagra occurring in their private practice. No one with a proper sense of values can feel that the results of a month's investigation of such a disease as pellagra can be of great importance, but the commission has requested that I present the case for dietary deficiency as I see it.

In the first place it should be stated that I regard the question as to whether pellagra is an infection or a deficiency disease to be entirely open. It does not appear to me that any evidence that can be regarded as proof of either hypothesis has yet been presented. It is rather a question of weighing the evidence and determining toward which

* Submitted for publication March 9, 1916.

* From the Army Medical School, Washington, D. C. This paper forms a part of the Third Report of the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* This report was written in September, 1914.

1. Vedder: Some Further Remarks on Beriberi, *Am. Jour. Trop. Dis. and Prev. Med.*, June, 1914, 1, 826.

hypothesis the bulk of the evidence points. The commission has been inclined to believe rather strongly that it points to the infectious origin of the disease. It seems to me that so far as I have examined it the evidence points at least as strongly toward a dietary deficiency, and it is this side of the case that will be presented here.

In order to understand what we mean by a dietary deficiency in pellagra it will be useful to present as clearly and concisely as possible the conception of deficiency diseases to which recent studies in beriberi and scurvy have led us. Briefly, this conception is that there are certain hitherto unknown chemical substances now called vitamins that are present in small but variable amounts in different foodstuffs, a definite supply of which is absolutely essential to the maintenance of normal metabolism. If a group of people live upon a diet which is deficient in any one of these vitamins, the corresponding deficiency disease is produced in a certain number of these people. Thus, if one hundred soldiers live on an exclusive diet of hard tack and bacon, after a definite depletion period a certain number of these soldiers will develop scurvy, because the scurvy vitamin is either entirely lacking or present in greatly reduced amounts in a diet of hardtack and bacon. If these soldiers are now given either fruits or fresh vegetables which contain this vitamin in relatively considerable amounts, they promptly recover. Equally, men who live on hardtack and bacon, but receive in addition a proper amount of fruit or fresh vegetables, will never develop scurvy.

Passing to beriberi, we find that if a number of people live exclusively on overmilled or white rice, which is deficient in the beriberi preventing vitamins, after a depletion period of about ninety days a certain number of these people develop beriberi. On the other hand, men who receive an undermilled rice which is practically the whole grain, never develop beriberi. It has been found by experimental evidence that the beriberi-preventing vitamins are present in considerable amounts in the external layers of the grain, which are removed in the milling process in the production of ordinary white rice. Furthermore, one of these vitamins has been extracted in crystalline form from the rice polishings removed from the grain, and it has been found that chemically it is probably a pyrimidin base hitherto unknown, but resembling thymine and cytosine in many of its chemical properties.

It should be noted that a deficiency disease is something radically different from malnutrition as the term is generally understood. Thus it is possible that the soldiers living exclusively on hardtack and bacon may have received an adequate amount of proteins, fats, carbohydrates and inorganic salts, furnishing an ample amount of calories, yet they suffered from a disease with a clear-cut clinical picture, namely, scurvy, because of the deficiency of a certain definite chemical sub-

stance which is contained in fruit juices and fresh vegetables. Equally, men living on a daily diet of two pounds of overmilled or white rice, a little meat and cocoanut oil, may receive an adequate amount of proteins, fats, and carbohydrates, according to the acknowledged dietary standards, and yet suffer from a disease with another clear-cut clinical picture, namely, beriberi, because this diet is deficient in certain definite chemical substances, namely, the beriberi preventing vitamins. A deficiency disease is therefore not malnutrition in the ordinary sense, nor is it caused by underfeeding, according to the ordinary standards of physiologists, with regard to a sufficient and properly balanced dietary.

It should also be pointed out that each individual requires a definite quantity of these vitamins. These beriberi-preventing vitamins are present in meat, milk, eggs and similar foods, in relatively small amounts, and in very large amounts in beans, rice polishings, and some other foods. Now, if a number of people live on a rice totally lacking in beriberi vitamins, and in addition consume a definite amount of meat containing beriberi vitamins, which, however, is insufficient in quantity to furnish a sufficient amount of these vitamins, the typical disease will occur in these people, but after a considerably longer incubation period than would have been the case had they lived on rice alone. In order to protect completely from beriberi it is therefore necessary to consume the amount of vitamin essential for that individual's metabolism.

It is further to be noted that because of personal idiosyncrasy the amount of vitamin required is not identical for all individuals. It has been found in feeding experiments on men and animals that of a number of people fed on precisely the same diet, some people develop beriberi much more rapidly than others, while, for some unexplained reason, some individuals never develop it apparently, though these individuals would be exceedingly rare if the beriberi-producing diet were continued for a sufficient length of time.

Now, regarding these statements to be proved facts with respect to beriberi and scurvy, known to be deficiency diseases, we may ask if it is possible to consider pellagra as a deficiency disease? The evidence presented in answer to this query may be considered under the following heads:

1. What analogies exist between pellagra and the two proved deficiency diseases, beriberi and scurvy?
2. Can the evidence pointing toward infection be reasonably explained according to a deficiency hypothesis?
3. Is any deficiency demonstrable in the diets of pellagrins?
4. Can the great increase in pellagra during recent years be explained by the deficiency hypothesis?

ANALOGIES EXISTING BETWEEN PELLAGRA AND BERIBERI OR SCURVY

With regard to the clinical and pathologic phenomena found in these diseases, there are numerous analogies existing between the clinicopathologic picture of pellagra and scurvy, and also between that of pellagra and beriberi, particularly the latter. In pellagra, according to Roberts,² "during the outbreak the gums are inflamed, in common with the rest of the oral mucosa. They are tender, often spongy and easy to bleed, as in scurvy; around the lower incisors this condition is most noticeable. During the outbreak stomatitis is present, and reaches its acme at the culmination of the dermatitis and glossitis. The inner borders of the lips and cheeks are red, tender, raw and swollen, and this inflammation extends over the buccal mucosa to such an extent that eating and swallowing are difficult."

With regard to scurvy, Osler³ says: "Very soon the gums are noticed to be swollen and spongy, to bleed easily, and in extreme cases to present a fungous appearance. These changes, regarded as characteristic, are sometimes absent. The tongue is swollen, but may be red and not much furred." The mouth condition, therefore, while not at all identical in the two diseases, at least presents a certain similarity.

The gastro-intestinal lesions in pellagra and scurvy are analogous. In pellagra we have diarrhea, enteritis, colitis and proctitis. "As the disease advances, the entire alimentary tract becomes inflamed; gastritis, enteritis, colitis and proctitis are the foundations for gastric and intestinal ulceration, with blood, mucus, pus and increased putrefaction and fermentation."² "With acute cases and enteritis, ulceration may occur at any part of the large or small gut."²

In scurvy, "Ulcers are occasionally met with in the ileum and colon. Hemorrhages, into the mucous membranes are extremely common."³

There are similar nervous symptoms in pellagra and scurvy. In pellagra the mental symptoms are so pronounced and well understood that it is unnecessary to quote authorities. In general, they consist of retardation of the mental processes and a general feeling of depression that may shade into melancholia or other psychoses. In scurvy, "there are mental depression, indifference, in some cases headache, and in the later stages, delirium."³ Osler mentions scurvy as one of the diseases from which pellagra must be differentiated. No attempt is being made here to show that the two diseases are at all identical, but

2. Roberts: Pellagra, C. V. Mosby Co., St. Louis, 1912, pp. 30, 109, 117, 119.

3. Osler: The Principles and Practice of Medicine, Ed. 8, D. Appleton & Co., New York, 1912, p. 447.

to point out that there are certain resemblances in their symptomatology and pathology.

Suggestive similarities also exist between pellagra and beriberi. Thus we find that in beriberi the mucous membrane of the stomach and duodenum is frequently swollen and inflamed, with a high degree of hyperemia and numerous ecchymoses and erosions. It may be remembered that Hamilton Wright thought that the cause of beriberi was a primary duodenitis caused by an invading bacillus. The pathologic process found in the duodenum in beriberi is often, therefore, somewhat similar to the condition of the intestine in pellagra, though the lesion never appears to progress so far or to be so extensive in beriberi as in pellagra.

Similarities in the lesions in the nervous system and in the symptomatology referable to the nervous system in pellagra and beriberi can be distinguished. The pathologic alterations that occur in the cord in pellagra are profound and striking. Extensive degenerations have been described in certain cases in the posterior column and in the pyramidal tract, as well as more or less diffuse degenerations. It is of course possible that certain of these cases of pellagra may have suffered at the same time with well-known nervous diseases, such as tabes dorsalis or multiple sclerosis. It seems clear that a definite sclerosis cannot occur in pellagra, since the majority of pellagra cases recover, and this would be an impossibility if an actual sclerosis of the cord were present. But it seems certain that a majority of the cases of pellagra suffer from a certain degree of degeneration of both the cells and the fibers of the cord, because of the great constancy with which these lesions are found in cases at necropsy, and because almost all cases of pellagra show symptoms that are referable to changes in the cord. A few quotations will serve to illustrate this point. The following is from Roberts:

1. Tracts: The tracts of Goll and Burdach show degeneration and a profuse proliferation. These tracts are pale compared with the rest of the cord. Occasionally degenerate roots entering in lumbar region can be traced up into the dorsal region. There may be degeneration of the posterior roots and an increase in the connective tissue around these roots, with occasional thickening of the arteries. The degenerate areas in stained preparations show like small spots of ink spattered all over the posterior column.

2. Direct pyramidal tract: There is more or less degeneration and scattered areas from which the nerve fibers have disappeared. Occasionally swollen axis cylinders are found (Spiller).

3. Gray matter: There is pigmentation of the cells of the anterior and posterior horns. The reticulum of many of the cells is clearly evident, and the fibrils appear contracted and the cell smaller. The cells of the posterior horns appear degenerated from the cervical region downward, and especially are the cells in Clarke's column affected. Spiller found cells in the anterior horns in the lumbar region degenerate, the cell body swollen, the nucleus displaced to the periphery, dendrites gone and intense chromatolysis, etc.

The following quotation is from a necropsy on a patient dying of pellagra, from the report of the pellagra commission of the state of Illinois, 1911, page 29:

Nerve cells: Sections were examined from various regions of the cortex and also from different levels in the cord and medulla. Stained with methylene blue and cresyl violet, marked chromatolytic changes of an axonal type were found in the large pyramidal cells of the Rolandic region, but especially of the Betz cells. Of these latter, practically all show extreme changes. The cells are swollen and stain faintly, the nucleus is displaced and the nucleolus often stains poorly. The Nissl granules have largely disappeared, small collections of them remaining at the base of the larger processes along the edges of the cell, and often collected as a small mass around the nucleus. . . . In the spinal cord similar changes are found in some anterior horn cells at all levels examined, but the great majority of these cells appeared healthy. The most marked changes were found in the cells of Clarke's column, where the majority of them were undergoing chromatolysis and pigmentary degeneration. Chromatolytic changes were also found in the cells of the posterior root ganglia. . . . Marchi method: In the spinal cord there are a few degenerated fibers scattered diffusely through the white matter. Degenerated fibers are also present in both anterior and posterior spinal roots.

Now, if we compare this picture with the changes found in the cord in beriberi, we find that beriberi is characterized by the same scattered degeneration of fibers in the cord and similar changes in the cells of the cord.⁴ The anatomical changes found in the brain in pellagra have not been demonstrated in beriberi, but Funk⁵ has shown that chemical changes occur in the brain of fowls that have developed polyneuritis as the result of rice feeding.

Beriberi has for years been regarded as essentially a disease of the nervous system. This conception of beriberi is hardly correct, since it is essentially a deficiency disease, resulting in numerous bodily changes. But it appears that pellagra is quite as much essentially a disease of the nervous system as is beriberi. The following quotations illustrate this point:

There is a general conviction that pellagra is especially a disease of the nervous system. Wood⁶ says: "It is daily a problem with me and my colleagues to differentiate between myelitis of specific origin and similar pathologic conditions produced by pellagra."

Pollock and Singer⁷ show that many of the severe and fatal cases present the syndrome of central neuritis, which is a reaction of the central nervous system to severe intoxication.

Dr. E. B. Saunders very kindly furnished me with information as to the mode of death among pellagrins in the Columbia State Hospital. According to her

4. Vedder: Beriberi, Wm. Wood & Co., New York, 1913, pp. 37, 39, 42, and Plate V.

5. Funk: The Effect of a Diet of Polished Rice on the Nitrogen and Phosphorus of the Brain, *Jour. Physiol.*, 1912, xlv, 50.

6. Wood, E. J.: Treatise on Pellagra, D. Appleton & Co., New York, 1912, p. 228.

7. Pollock and Singer: The Histopathology of the Nervous System in Pellagra, *THE ARCHIVES INT. MED.*, June, 1913, xi, 565.

observations in a series of eighty-eight fatal cases, sixty-four, or 74.7 per cent., died with central neuritic symptoms; nineteen, or 21.6 per cent., with appearances of simple exhaustion, and five, or 5.6 per cent., terminated suddenly from some unknown cause. In all severe cases there are evidences of irritable weakness in the nervous system, such as tremors, exaggeration of tendon jerks, increased myotatic irritability, etc., entirely comparable to those met with in other severe intoxicative conditions, such as tuberculosis.⁸

It was exactly such changes in the nervous system that caused beriberi to be considered for many years as an intoxication. Now that we know that beriberi is a deficiency disease, it is apparent that these changes in pellagra are quite as likely to be due to deficiency as to intoxication or infection. The fact that the spinal fluid in pellagra is normal, points toward deficiency, since it seems improbable that such extensive changes in the cord could occur as the result of an infection without producing the corresponding changes in the spinal fluid. Even the skin lesions which are so characteristic of pellagra may be referable to changes in the cord. Otherwise, how can we explain the marvelous symmetry that is practically the constant characteristic of this symptom?

But without attempting to strain the analogy, enough has been said to show that pellagra shows marked similarities in both pathology and symptomatology to beriberi and scurvy, two deficiency diseases. While it would be foolish to assume that therefore pellagra must also be a deficiency disease, this possibility is at least suggested, while on the other hand it may be stated that there is nothing in the pathology or symptomatology of pellagra of such a nature as to render it impossible to conceive of their production as a result of a dietary deficiency. Similar and equally marked changes are produced as the result of two known deficiency diseases.

Analogies exist between the epidemiologic data in pellagra and beriberi. Pellagra, like beriberi, is a disease intimately associated with poverty and poor diet. The present commission has classified 277 cases of pellagra according to economic conditions as follows:

Squalor	2
Poverty	28
Necessities	200
Comfort	41
Affluence	6
Total	277

This is sufficient to show that among the people at large its distribution is chiefly among the poorer classes. It is admitted by the commission that the diet of these poorer people is far from satisfactory,

8. Singer: Mental and Nervous Disorders Associated with Pellagra: Second Progress Reports, Thompson-McFadden Pellagra Commission; THE ARCHIVES INT. MED., 1915, xv, 121.

and the commission is inclined to lay a great deal of stress on the importance of diet as a contributory factor in the production of pellagra.

Like beriberi, pellagra shows an extraordinary frequency in hospitals for the insane and in similar institutions where a large number of people live under comparatively good sanitary conditions, but where the diet is by no means above reproach. At the same time, like beriberi, it is exceedingly rare for doctors, nurses or attendants, living in close personal contact with these cases, but on a different dietary, to acquire pellagra. Thus Singer⁸ says.

Pellagra shows an extraordinary frequency in hospitals for insane. This fact of almost universal experience is well illustrated by the situation at Milledgeville, Ga. If we accept the proportion of certifiable insanity for Spartanburg County as approximately correct for the state of Georgia, this would mean that in 1910 there were approximately 900 pellagrins (this figure is probably far too small), or 3.4 per 10,000 of the population. On the other hand, the average daily population of the hospital was 3,276, with 114 cases of pellagra, or 348 per 10,000, practically 100 times as many as in the population outside. Experience in Illinois would tend to bear this out. There are several possibilities:

1. If infectious, these hospitals are endemic foci with favorable opportunities for transmission.

2. Deficient dietary or food intoxication may exist.

3. Conditions of life or constitution of persons confined in such a hospital may be such as to especially favor the onset of pellagra, whether the cause be a living virus, deficiency or intoxication.

In discussing these possibilities, it must be conceded that the only explanation for a special focus of infection in such a hospital would be the collection together of a large number of infected individuals sent to the hospital because of the occurrence of "insanity." This would not explain the sequence of events at the Peoria State Hospital and other institutions of like character in Illinois where the outbreaks appeared to start in these widely separated localities while the number of cases in the state generally was certainly small.

Some explanation is also needed for the rarity with which doctors or attendants in these institutions become affected. I know of no instance in Illinois. In Georgia but one was reported (J. E. H., white male attendant, on June 19, 1913) in the years from 1910 to July, 1913.

It appears, therefore, that it is extremely difficult to account for the peculiar distribution of pellagra in these institutions on the basis of an infection, while it is rather easy on the hypothesis of a dietary deficiency. As a matter of fact the dietary at Peoria was admitted to be poor, and soon after it was radically improved pellagra disappeared.

Still further, as Singer says:

It is quite within the bounds of possibility that the actual relation between the functional psychoses (including dementia praecox) and pellagra is somewhat the reverse of that more usually accepted. That the defective construction, whatever it be, which is responsible for the poor adaptability and peculiarity of make up, indicated by the particular stamp of these disorders, predisposes to the development of pellagra. It is certainly a fact that the disease is extremely frequent among the chronic insane, most of whom represent late stages of the dementia praecox personality.

This is exactly what Bondurant⁹ found to be the case with regard to the distribution of beriberi at the Alabama Bryce Insane Hospital. Every one of the seventy-one patients attacked was the subject of some psychic degenerative form of mental disorder. It is apparent, therefore, that there is some close relation between such psychic states and a tendency to acquire a deficiency disease. A possible explanation of this fact is the well-known indisposition of many such patients to eat a correct or sufficient diet. This hypothesis would explain Singer's observation of the tendency of this class of persons to develop pellagra.

In Italy at least, pellagra appears to bear somewhat the same relation to the consumption of corn that beriberi bears to the consumption of rice. The striking analogy, which every one admits, and which has led the Italian investigators for many years to believe that pellagra is caused in some way as the result of a corn diet, needs no further discussion.

The theories promulgated as to the cause of pellagra bear a striking resemblance to the history of the investigations into the cause of beriberi. Like beriberi, when first discovered many attributed it to an improper diet. After finding apparent inconsistencies in this explanation, in each disease the pendulum has swung to intoxication, infection, and finally back to deficiency again. Pellagra, like beriberi, has been investigated carefully for a number of years in the endeavor to discover some micro-organism or toxin responsible for this condition. All such efforts have been futile. This, of course, like other analogies, proves nothing, but it is at least suggestive. Such analogies might be multiplied and carried farther, but no good purpose would be served by doing so, since no definite evidence is to be obtained in this way.

CAN THE EVIDENCE POINTING TOWARD INFECTION BE EXPLAINED ON THE DEFICIENCY HYPOTHESIS?

Let us look into the character of the disease. The peculiar pathology and symptomatology of pellagra has undoubtedly caused some observers to come to the conclusion that pellagra is a toxemia or is infectious. At first glance it does seem difficult to believe that such pronounced lesions can be caused by a mere dietary deficiency. But we have already discussed the resemblances in the pathology and symptomatology of pellagra as compared with beriberi and scurvy and have come to the conclusion that if dietary deficiency can produce the pathologic condition observed in beriberi and scurvy, it is quite possible that a different deficiency could produce the changes observed in pellagra.

9. Bondurant: Report of Thirteen Cases of Multiple Neuritis Occurring Among Insane Patients, *Med. News*, London, 1896, lxix, 365; Endemic Multiple Neuritis (Beriberi), *New York Med. Jour.*, 1897, lxix, 685, 728.

But beyond this, the definite tendency seen in pellagra to self-limitation of the attacks in the absence of specific therapy, and during the continuance of presumably the same defective diet that produced the disease, appears to some to bear a very suggestive resemblance to the course of an infectious disease. Most decidedly an opinion exists that if the disease were due to a deficiency, it could not be self-limited while the deficiency exists. But is pellagra really self-limiting while the deficiency exists? Granting for the sake of argument that pellagra is a deficiency disease, we have been in total ignorance as to which foods contain the necessary vitamins and which foods are totally deficient. How then is it possible to say that the patient has not received some nourishment which has supplied the deficiency and that the improvement is not in reality due to this fact? It would not be possible to make such a statement except in the case of a patient fed on water alone, and such cases must be exceedingly rare. If the patient is in such condition as to make it possible to take only liquid nourishment, he still can and probably does receive soups, milk, albumin water and similar diets, any one of which may, so far as we know, be responsible for the change for the better.

The converse of this proposition has also been stated, namely, that patients with pellagra sometimes become worse and often die in spite of the fact that they are receiving a most excellent diet. But while it may have been an excellent diet generally speaking, it may not have been particularly rich in the necessary vitamins, or the patient may have been unable to assimilate them. Further, we know that patients with dry beriberi often become worse and die, even though they be fed on beans, rice polish and other substances that we now know will prevent the development of beriberi. This is a well authenticated fact, and the probable explanation is that the lesions in the cord and nervous system generally have proceeded to such a point that death is imminent and may occur at any time. In this form of beriberi the road to recovery is long and up hill, and on any diet only occurs after several months. It is clear, therefore, that the patient may die before the slow process of recovery has succeeded in patching up his serious lesions. Is not the same thing conceivable and even probable in pellagra, granting that it is a deficiency disease? Aside from theoretical reasoning, it is an observed fact that beriberi patients have their ups and downs either in their natural surroundings or in a hospital. In some the disease appears to be quite as naturally self-limited as is the case in pellagra. Manson describes this in his most graphic and charming style as follows.

As the visitor watches the progress of the cases he will be astonished that those which he thought examples of locomotor ataxia, or of progressive muscular atrophy, or of ascending spinal paralysis, gradually improve, begin to walk about,

and finally quit the hospital quite well. He will be astonished to see, after perhaps a profuse diuresis, the bloated carcass that could hardly turn itself in bed rapidly shrivel to little more than skin and bone, and assume all the appearances of the atrophic cases; and later, perhaps after many months, become rehabilitated, and, in due course, walk out of the hospital quite well. He will notice that the cardiac bruits come and go; that the degree of dilatation of the heart is subject to fluctuations; that what seemed organic disease completely disappears. But he will also be astonished, as he goes his rounds, to see so often empty beds where the day before lay men whom he considered by no means seriously ill, certainly not dying. Some day he will come on a patient whom the previous day he thought to be by no means seriously ill, actually in extremis. The poor fellow is propped up in bed, is struggling for breath, his face is purple, his eyes are starting out of his head, his whole attitude is expressive of the utmost distress—in a short time the patient is dead.

This account was written prior to the days when the relation of diet to beriberi was known. I have no doubt that Manson would have thought that all of his patients were receiving an excellent diet, yet some of them recovered, and some died in a most unaccountable manner. It is probable that at this day we cannot explain all of these peculiarities by demonstrated changes in the patient's diet. Some must be ascribed to the personal peculiarities of the patient and to the particular pathologic changes that have occurred in that patient. In view of the fact that beriberi has acted in this peculiar way, shall we say when we observe the same kind of peculiar and unexplainable occurrences in pellagra that this points toward infection? By no means. It points equally or more toward a deficiency disease that acts just as beriberi acts.

But again, it is objected that pellagra appears in the spring and improves during the summer and fall, only to recur again next spring. This fact appears to point distinctly toward the dietary hypothesis. The peculiar tendency to recurrence during the late spring, May or June, if explained according to the infection theory, presupposes an infection that acts differently from any known infection; one that is dormant during the winter months only to break out with fresh fury in the next spring, and not only once, but again and again. It is safe to say that we know of no infection at present that acts in this way; but beriberi acts in precisely this fashion. It not only appears more commonly during certain well-known seasons of the year, but individual patients are subject to frequent recurrences during these seasons. The dietary habits of the people undergo considerable change with the seasons. For instance, in the general population more meat is eaten in the winter than in the summer. But is it not quite possible that during the winter the poor, who suffer chiefly from pellagra, live mainly on flour, cornmeal, canned beans, salt pork, etc.; that they are thus subject to a deficiency, which, after a depletion period of several months, produces lesions in the spring; and that when fresh vegetables and fruits appear in the market in the spring and summer the con-

sumption of such food supplies the deficiency, and the disease improves, only to recur in the following spring after the patient has once again been subject to the same deficiency? This conception is at least as plausible as the conception of an infection that can produce such peculiar seasonal recurrences with intervals of apparently perfect health.

Is contact or personal association with cases of pellagra an etiological factor? In about 90 per cent. of the cases of pellagra studied, this commission has established the fact that some degree of personal contact or association with a previous case of pellagra can be traced. This fact, which at first glance appears to argue strongly in favor of the infectious nature of the disease, is in reality of little significance. For in the first place a large number of these contacts, 43.5 per cent., have occurred among members of the same family, who have presumably lived upon the same diet, and if the cause of pellagra were a dietary deficiency it would be expected that several cases would frequently develop in one family. With regard to the remainder of these cases, 46.5 per cent., in which contact with an antecedent case outside the family has been demonstrated, it must be pointed out that pellagra has become so common in many parts of the South that practically every one has come into some contact or association with a case of pellagra. Pellagrins ride in the street cars, they peddle vegetables and fruits, they frequent moving pictures and other public gatherings and come in contact with normal individuals in all the numerous ways possible in our society. The fact that a very large part of the population has in these ways been in contact with cases of pellagra without developing the disease necessarily detracts from the importance of contact as an etiologic factor. Further, in institutions those persons in closest contact with pellagrins, namely the doctors, nurses and attendants, seldom acquire the disease.

Is the tendency of pellagra to vary with the density of population an indication of infection? The commission says:¹⁰ "The conception that pellagra is an infectious disease in some way transmissible from person to person seems to us to be strongly supported by many of the field observations. The higher incidence of pellagra in the more populous districts and the indications of its occurrence in definite foci are in accord with this idea." They find that the cotton mill village population gives a rate of prevalence of 184 per 10,000 against 19 per 10,000 for the remainder of the county and against 16 per 10,000 for the rural sections alone. It is only fair to add that on page 26 the commission says: "Further evidence that density of population alone is not accountable for the greater prevalence of the disease in mill villages is found in Spartanburg City itself. There the mill villages,

10. First Progress Report, Thompson-McFadden Pellagra Commission, p. 11.

which are continuous with and an integral part of the city, present a rate of 142 per 10,000, whereas the remainder of the city population, living under approximately the same condition of congestion, gives only 29 per 10,000. Furthermore, the non-mill-village population within the city, with a density which is certainly over 3,000 per square mile, shows almost exactly the same prevalence of pellagra per 10,000, as does the strictly rural population of the surrounding township, with only 90 inhabitants per square mile." This seems to me to definitely dispose of the idea that density of population alone bears any relation to the spread of pellagra. It should furthermore be noted that many authorities claim that pellagra is distinctly a rural disease and stops abruptly when it reaches cities.² It may be mentioned in passing that the higher incidence of pellagra in the mill villages would be readily explainable according to the deficiency hypothesis by assuming that the mill village population was a rather homogeneous group of the community, and as a group, is poorer economically and lives on a poorer class of food. As a matter of fact, this assumption is correct. The occurrence of the disease in definite foci does not therefore afford any proof that density of population alone influences the incidence of pellagra.

Is proximity of domicile a factor in the occurrence of pellagra? The most important evidence collected by the commission pointing toward the infectious origin of pellagra is its study of the domicile of cases. The commission shows that of 819 nonpellagrin individuals who lived in the house where pellagra existed at the time, fifty-four, or 6.59 per cent., acquired pellagra, while in the 3,201 nonpellagrin individuals who lived next door to a house in which pellagra existed, fifty-five, or 1.72 per cent., developed pellagra; of the 3,105 persons who lived in houses farther away than next door to a pellagrin, sixteen, or 0.52 per cent., contracted the disease. The new cases of the disease developed almost exclusively in small foci within which one or more cases of the disease already existed.

Can this incidence of cases be explained if the disease is not infectious, but caused by dietary deficiency? In the first place it will be at once seen that zone 1, in which 6.59 per cent. of the exposed individuals acquired pellagra, consists of those people living in the same house with a pellagrin. If the disease were of dietary origin, the majority of the inhabitants of this house, presumably living on approximately the same diet, would all be exposed to the same deficiency, and a high proportion of additional cases would develop. The considerable number of cases occurring in the first zone can therefore be explained quite as easily in accordance with the dietary as by the infection hypothesis. But with this zone eliminated, the domiciliary argument has lost much of its force, since only two zones are left and the inci-

dence of pellagra in the second zone was only slightly more than three times as frequent as the third zone. A possible explanation for the higher incidence of cases in the second zone may be as follows: Pellagra is much commoner among the poor than among the well-to-do. Now in all of these villages there is probably a natural tendency for the well-to-do to live in certain parts of the village, and for the poorer workers to live in certain localities and streets. This is a human tendency which may be less marked in mill villages than it is among the population of a city, but still it exists. The reason for this segregation of the poor lies in various economic factors, such as possibly the cheaper rent in one section of the town, and also in the tendency for like to seek like. Well-to-do people naturally select a house next to well-to-do neighbors, rather than next to a poverty-stricken neighbor. This is a human tendency that is just as definite as the tendency for water to seek its level. There is, further, in most of these towns a considerable proportion of floating population. These people do not reside permanently at any one mill, but move from mill to mill as they become discontented. A very considerable proportion of the wages of these transients is consumed in their frequent moves, they are generally a less efficient type of worker and receive on this account smaller wages, and they are, as a general rule, distinctly lower in the economic scale than the permanent residents. In many of the villages a certain street or locality is set apart for new comers, and they are only permitted to move to a better part of the town after they have "made good." Now if this tendency of the poor to become segregated be granted, and if pellagra is due to a dietary deficiency, it follows that it will occur most often in the streets or localities more frequented by the poorer workers, and less frequently among those streets and localities inhabited by the well-to-do. And if such a grouping of the population and of the disease occurs, the second zone, namely, the houses contiguous to a case of pellagra, would naturally show a higher incidence of the disease than the houses at a greater distance. The zone distribution of cases of pellagra in such villages cannot afford any conclusive evidence that the disease is an infection, while it is possible of explanation on the other hypothesis.

Moreover, it appears to me that to accept this zone distribution of cases as pointing to an infectious agent as the cause of pellagra involves us in an inconsistency. We must necessarily assume that the infectious agent is conveyed in some manner from house to house, and also, from the frequency with which contiguous houses are attacked that it is susceptible of being distributed with a considerable degree of certainty. In other words, we must assume that the organism causing the disease must be very highly infectious if it is capable of making it dangerous to live next door to a case of pellagra. Yet

in institutions pellagra in a doctor, nurse or attendant is so rare as to be a curiosity. We have then an infection so powerful that it often spreads from house to house, and yet which is powerless to attack attendants performing the most intimate of personal services. Such a peculiar incidence is conceivable in a disease carried by an insect, if the hospital attendants were protected from that insect. But as the method of transmission is unknown, measures to prevent insect transmission could not have been intelligently adopted in these institutions, many of which are infested with bedbugs, lice, biting flies and mosquitoes.

Is there a tendency of pellagra to occur in that part of a community having a primitive system of disposal of excreta and to be absent in the portion having a proper sewer system? The commission has shown that pellagra in Spartanburg is much commoner in those sections of the city having privies than in those sections of the city having a sewer system. The sewer system runs throughout the business sections and better residence districts, while the poorer residence districts, including the several foci of mill workers, are supplied with unscreened privies. Since, in general, it is the poor people who have the privies, it is apparent that poverty and a poorer dietary cannot be excluded as the possible factor producing the disease. The commission points to the epidemic of pellagra occurring in Peoria as an instance of the occurrence of the disease in a well sewered institution, but thinks that the disease in this case may have been spread by contact. While freely granting this, we must see that the occurrence of such an extensive epidemic of pellagra in a well-sewered institution must necessarily detract from the importance of the sewer system alone as a factor in reducing the prevalence of pellagra in the sections of Spartanburg it supplies. It should further be remembered that as pellagra in the Peoria institution disappeared after a radical change for the better had been made in the dietary, together with the enforcement of segregation of pellagrins, the disappearance of the disease can not logically be attributed to the latter factor alone. I realize that this brief discussion of one or two isolated instances can not do justice to the large number of observations accumulated by the commission on this point, but I think that the commission does not believe that they have any direct proof that pellagra has disappeared as the result of improved methods of conservancy alone.

The commission has been inclined to believe that the disease is not of dietary origin because their investigations have failed to implicate any special food as the causative factor.¹¹ Thus, in the case of beriberi,

11. Siler, Garrison and MacNeal: A Statistical Study of the Relation of Pellagra to Use of Certain Foods and to Location of Domicile in Six Selected Industrial Communities, *THE ARCHIVES INT. MED.*, 1914, xiv, 293.

in those countries where the disease is endemic, it is very closely associated with the consumption of overmilled rice. No such striking parallel has been brought out by the observations of the commission in this country. Corn, of course, has been implicated in other countries, particularly in Italy, but the commission has shown that in this country the incidence of pellagra is relatively higher among those using cornmeal rarely or never. Thus, of those using cornmeal daily, 3.13 per cent. were pellagrins; of those using it habitually, 4.3 per cent. were pellagrins; and of those using it rarely or never 6.02 per cent. were pellagrins. Obviously, they think that corn as a causative factor must be dismissed from further consideration. Similarly, they find that of eighty-nine persons using canned foods daily, none were pellagrins; while of those using these foods habitually, 3.25 per cent. were pellagrins; and of those using them rarely or never, 4.12 per cent. were pellagrins.

Again, if the disease were a deficiency disease, fresh meat, milk and eggs might be supposed to supply this deficiency. They found, however, that of the eighty-two persons in families using fresh meat daily, four, or 4.88 per cent., were pellagrins; of the 2,591 individuals in families using this food habitually, 3.74 per cent. were pellagrins; and of the 263 persons never using fresh meat, only four, or 1.52 per cent., were pellagrins. Similar figures were obtained with regard to the use of eggs. The commission is therefore inclined to believe that the disease is not caused by a dietary deficiency.

It appears to me that this evidence is not at all conclusive for the following reasons: 1. It does not consider in sufficient detail the quantities of the various foods used. In an investigation of this kind it is important to know the relative quantities of the different food-stuffs used. It has been found in the course of experimental work on beriberi that if fowls are fed exclusively on overmilled rice, they develop polyneuritis after about thirty days. Now if in addition to polished or overmilled rice these fowls are fed 10 gm. of meat daily, it was found that these fowls developed polyneuritis with just as much certainty, but only after a longer depletion period, about fifty days. In other words, the meat contained a certain amount of protective vitamins. If consumed in sufficient quantity, it would have protected the fowls completely against the disease. But 10 gm. was a quantity insufficient to afford this complete protection. The fowls still suffered from the same deficiency, though not to so pronounced a degree, and the clinical manifestations of the disease therefore appeared after a longer depletion period. Experience has shown that a similar relationship exists with regard to the quantities of foods consumed and beriberi in man.

If pellagra is a deficiency disease, a similar relation undoubtedly exists between the occurrence of the disease and the quantities of certain foodstuffs consumed. Thus, let us suppose that the disease is caused by a deficiency occurring in wheat flour and that the chemical substance or vitamin deficient in wheat flour is present in a certain small amount in eggs. It follows that if a man ate a pound of bread and an egg daily he might still suffer from the deficiency because one egg would contain an insufficient amount of vitamins to make up for the deficiency in the flour. On the other hand, if the man ate a pound of bread and four eggs daily, he might be completely protected.

Now in their dietary study the commission has classified the users of various foodstuffs into those eating them daily, or habitually, and those eating them rarely, or never. This, however, is by no means the same as an exact quantitative determination of the amounts of food used. The man referred to above could have honestly stated that he ate eggs daily, and this may have happened in a considerable number of instances, which might explain why pellagra was found to be frequent among those who used eggs daily. The Filipino who develops beriberi does not live on rice alone. He also eats a small quantity of fish. Many of them eat two pounds of rice daily, and at each of the three meals will also eat a fish the size of a small herring. This man eats fish daily, yet he develops beriberi. Are we therefore to conclude that because he eats fish daily and develops beriberi that fish can be of no importance in preventing beriberi? It is impossible to draw conclusions as to the relative value of different foodstuffs in preventing a given disease except from a quantitative study, and such quantities are not supplied by a statement that the food under consideration is eaten daily or habitually; in fact such observations may be exceedingly misleading.

2. In the commission's study of the diet a very large number of individuals have been consulted with regard to their use of certain foods. When these statistics have been compiled, each foodstuff has been considered singly, that is, the influence of corn meal or of eggs, etc., with regard to pellagra has been considered separately. But in order to determine if the diet consumed by a given individual is deficient, the total diet must be considered, or otherwise an erroneous conclusion may be deduced. For instance, we may find that five individuals consume corn meal daily and none of them suffer from pellagra, while five other individuals never consume cornmeal and all five have pellagra. Shall we assume that cornmeal is of no importance in relation to pellagra? This would be erroneous, because the five individuals eating cornmeal daily may also eat a large number of other foods which supply the deficiency, while those who never eat cornmeal and develop pellagra may be living too exclusively on some other food,

such as wheat flour, which is also deficient in proper vitamins. Evidently, therefore, in any community such as this, where a considerable number of different foodstuffs are consumed by the population, an idea as to the existence of a deficiency can be obtained only by considering the total diets of individuals suffering with pellagra as compared with total diets of the healthy part of the population, and not by the consideration of single items of the dietary.

3. The commission has not discussed sufficiently the possibility that wheat flour is the foodstuff that is mainly responsible for the deficiency. They say: "Wheat flour was used daily by every family in the population studied. No distinction between pellagrins and nonpellagrins could be ascertained in respect to this dietary element." It appears to me, as will be seen farther along, that wheat flour is certainly an excessively large component in the diets of the pellagrins studied, as compared with the relative amounts of other foods used. Flour has long been known to be deficient in the scurvy vitamins. It has been shown by Little¹² that white wheat flour is deficient in the beriberi-preventing vitamins. Is it not also possible that if pellagra is a deficiency disease it is also deficient in the pellagra vitamins?

None of the evidence discussed here is of such a nature as to enable us to say that pellagra is not infectious or is a deficiency disease. But it does seem to me as if the commission is inclined to dismiss the dietary deficiency hypothesis from further consideration a little too hastily.

IS THERE DEFICIENCY IN THE DIET OF PELLAGRINS

With these conditions in mind, the investigation was focused in an attempt to determine whether any deficiency could be demonstrated in the diets of pellagrins. For this purpose a number of pellagrins were visited and inquiries made as to their diet, and particularly with regard to their diet during the winter preceding the first attack of the disease. The information so obtained may be summarized as follows:

The diet of pellagrous mill workers and other relatively poor individuals was investigated as follows:

CASE 1.—Miss T., mill operative: Breakfast: Hot biscuit, butter and molasses; rice occasionally; canned salmon frequently; eggs a couple of times a week; coffee; glass of milk at times.

Dinner: Meat, usually bacon boiled with vegetables; had fresh beef once or twice a week, fried and usually overcooked; chicken or rabbit about once a month; had vegetables, such as Irish potatoes, sweet potatoes; in winter used canned vegetables, but in summer had string beans, corn, peas, onions, etc.; cornbread made of shipped meal.

12. Little: Beriberi Caused by Fine White Flour, *Jour. Am. Med. Assn.*, 1912, lviii, 2029.

Supper: Cornbread and buttermilk; drank about a quart of milk daily (her estimate); ate a good deal of candy and always had plenty of fresh fruit. This family (father and mother and seven children from 20 years of age to 13 months) purchased each month: 100 pounds wheat flour, 2 bushels corn meal, 1 bushel Irish potatoes, hominy and rice as desired from time to time, and no account kept.

CASE 2.—Mr. T., father of Miss T.: Will not eat fresh beef, but otherwise eats the same diet as given above.

CASE 3.—Mrs. H., housewife in mill village: Breakfast: Biscuits or bread; salmon twice a week, other mornings bacon; coffee; eggs rarely.

Dinner: Tomato soup; salt pork boiled with vegetables, usually cabbage, sometimes string beans; Irish potatoes; fresh meat only on rare occasions in the winter, never in summer; biscuit or corn bread.

Supper: Bread with milk when they can get milk; bread is the main part of supper with anything left over from dinner; occasionally something canned. There are nine in the family, with seven children from 14 years to 4 months, and they purchase every month: 100 pounds flour, 1 bushel corn meal, 1 peck Irish potatoes.

CASES 4 and 5.—Bertha, aged 9, and Bessie, aged 6, children of mill operative. Breakfast: Bread, butter and molasses; canned salmon occasionally; eggs once every two weeks or a month; coffee.

Dinner: During winter have a little steak or fresh pork occasionally, otherwise no meat; dinner consists chiefly of Irish potatoes with boiled vegetables, usually cabbage; cornbread or biscuits; a glass of milk.

Supper: Cornbread and one glass of milk with everything left from dinner; fruit in summer, but none in winter. For the seven in the family, five children from 16 to 4 years of age, they purchase each month: 75 pounds flour, 2 bushels cornmeal, 3 pecks of potatoes.

CASE 6.—Mrs. B., housewife of mill operative: Breakfast: Biscuit, butter, jelly and syrup; coffee, bacon and eggs every week or two.

Dinner: Chicken three or four times during winter, otherwise no meat except salt pork; potatoes, cabbage or beans, tomatoes once in a while; cornbread.

Supper: Cornbread and what is left from dinner. For the eight members of the family, six children from 18 to 4 years, they purchase each month: 50 pounds flour, 1 bushel cornmeal, 2 pecks of potatoes.

Mrs. B. came from a farm on January 29 and developed pellagra about June. When she lived on the farm her diet was as follows:

Breakfast: Biscuits, butter; one or two eggs once or twice a week; chicken every week or two; fresh pork occasionally at hog killing.

Dinner: Had more vegetables than above, and one glass of buttermilk every day; had more fruit than now.

Supper: Same as above, except that she always had plenty of milk. She says she lived better on the farm.

CASE 7.—Mrs. B., wife of mill operative: Breakfast: Rice, oatmeal occasionally, hominy frequently, bread, butter and jelly; coffee; eggs several days a week; in winter fresh meat once a week.

Dinner: Irish potatoes, bacon and vegetables, beans, peas or turnip greens; bread and butter.

Supper: Irish potatoes, cornbread sometimes, otherwise wheat bread, butter, and anything left from dinner; drinks no milk; has a chicken occasionally, but not often.

CASE 8.—Mrs. D., wife of mill operative: Breakfast: Hominy or oatmeal; ham or bacon; eats an egg perhaps two mornings a week; bread, butter and postum. Says chief part of her breakfast is always bread and butter.

Dinner: Irish potatoes; in winter has beans; says she does not care for meat and practically never eats it; bread and butter and usually pie or cake; main part of dinner is the beans and potatoes.

Supper: Same as dinner; drinks about two glasses of buttermilk a day; has plenty of fruit; family of three adults, purchases each month: 100 pounds flour; 1 peck cornmeal, 1 peck potatoes.

CASES 9 and 10.—Mrs. A and son, mill operatives: Breakfast: Bread, coffee, bacon, butter sometimes.

Dinner: Irish potatoes, bulk of meal, bacon and cabbage; cornbread made from shipped meal.

Supper: Cornbread and milk; half gallon of milk used for family of five; no fresh meat.

CASE 11.—Mrs. K., inmate of county home. Only case to develop at this home, where she has been an inmate for three years. Breakfast: Grits or rice; biscuit, gravy and coffee; did not eat eggs or meat.

Dinner: Cabbage or beans with one or two Irish potatoes; salt meat usually, but beef or chicken on Sundays, when she ate a fair portion; cornbread; sometimes drank milk for dinner.

Supper: Cornbread and milk; drank one glassful of sweet milk; is particularly fond of cornbread and milk, though she does not drink much milk, rarely more than two glasses a day.

CASE 12.—Mrs. McC., wife of mill operative (Newry): Breakfast: Salt pork, biscuits and molasses, butter and coffee; does not eat eggs.

Dinner: Had fresh meat perhaps once a week, but did not eat much; ate a good deal of cornbread with salt pork and cabbage or turnips; perhaps a glass of milk.

Supper: Cornbread and milk, sometimes vegetables left from dinner; had apple pie or cake; no meat.

CASE 13.—Mrs. E., wife of mill operative (Newry): Breakfast: Biscuits with butter and syrup or jelly; coffee; eats an egg about once a week.

Dinner: Irish potatoes, sometimes tomato soup (canned tomatoes) and beans; have meat sometimes, but she does not eat it, never did like it; biscuits or cornbread, but she ate biscuits mostly; milk, possibly two glasses; pie often.

Supper: Bread and butter or syrup and milk.

Says she drank about a quart of milk a day. Has had nine children. Disease first noticed just after birth of next to last child.

CASE 14.—Mrs. A., wife of mill operative (Newry). Breakfast: Bread and butter or jelly; sometimes eats an egg, but often does not have one for several weeks; says breakfast is usually a biscuit with jelly and coffee.

Dinner: Cornbread with beans or cabbage; does not eat fresh meat; eats more cornbread than anything else, with a glass of milk.

Supper: Cornbread and a glass of milk. Husband works in mill and receives \$1 per day. Has two children who go to school. Total income less than \$30 a month.

CASE 15.—Mrs. W., widow living at Cherokee, farmer. Breakfast: Biscuit, butter and coffee; no meat, no eggs.

Dinner: Cornbread and glass of milk; sweet potatoes often; peas occasionally, other vegetables seldom. Killed one hog last winter, and had fresh pork one week, after that nothing but salt meat.

Supper: Bread and a glass of milk; practically nothing else. Mrs. W. works in the fields herself on this diet.

Such cases might be multiplied indefinitely. A considerable number of other victims of pellagra were seen who lived on such a scanty and one-sided diet. In general, it may be said that the great bulk of the food of these poorer pellagrins consists of wheat flour, cornmeal, potatoes, salt pork and boiled vegetables, and that during the winter even these latter are scarce and consist chiefly of beans and cabbage.

In some instances a considerable amount of canned meats and vegetables were used, but most of the pellagrins did not use these to any extent. It will be seen that the great bulk of the food consisted of carbohydrates and that protein foods such as meat, milk and eggs are relatively little used. It is also important to notice that wheat flour, cornmeal and salt meat are deficient in both scurvy and beriberi vitamins. Potatoes possess the scurvy vitamin, but are relatively very low in beriberi vitamins. It has been demonstrated that the vitamins present in canned goods may be destroyed by the sterilization to which they are subjected. It is therefore clear that these people are living in great part on foodstuffs the continued and disproportionate use of which will produce either beriberi or scurvy, or both. It may be asked why these people do not suffer from these diseases. This is because they all eat sufficient fruit or fresh vegetables to protect them from scurvy, while many of them eat peas and beans frequently. These rank as one of the best preventives of beriberi known. But it is quite reasonable to suppose that possibly there is some third deficiency existing in wheat flour, cornbread, etc., from which they are not protected by these additions. Generally speaking, and with the exception of meat, which is not used largely by the poor, the diet is much more limited in the winter. If pellagra is a deficiency disease, it is during these winter months that it develops and the symptoms appear in the spring. At about that time eggs, milk, fresh vegetables and fruits become abundant and cheap, are used in considerable quantities as compared with the winter diet, and the patients for the most part recover, only to develop another recurrence the following spring after another winter on a comparatively limited diet. It is clear that such observations, while exceedingly suggestive, would not prove the case for deficiency, particularly as sanitary conditions, contacts, etc., were not studied in these cases. It was very desirable, however, to see if this theory could be readily disproven.

Accordingly the diets were investigated in a number of well-to-do cases, for the dietary enthusiast is at once asked the question, How do you explain the cases occurring in well-to-do or even wealthy families, the members of which eat the best of everything? As many of these cases as possible were investigated, but their number is necessarily small. All were in good circumstances, having a sufficient salary and living in good sanitary surroundings with a water carriage system of sewer disposal. No attempt, however, was made to rule out contact with other cases, although in some cases such contact was denied.

CASE 1.—Mr. T., a well-to-do farmer, owning his own farm. Breakfast: Hominy, biscuits, butter, molasses and coffee; same the year round.

Dinner: Salt pork with vegetables; usually cabbage or turnips in winter, sometimes peas or beans; sweet potatoes from August to January; Irish potatoes, biscuits and cornbread.

Supper: What remained from dinner with cornbread; drank about a quart of buttermilk a day; seldom ate eggs, and had a chicken about once a week; had fresh pork occasionally in the winter at hog killing time.

This family of seven, with five children, purchased monthly: 75 to 100 pounds of flour, $1\frac{1}{2}$ bushels of cornmeal, sugar and coffee.

CASE 2.—Mrs. T., wife of the man in Case 1. Ate exactly the same as above, except that she had steak about once a week for breakfast and ham several days a week for breakfast; ate an egg about twice a week. Dinner and supper the same except that she ate more Irish potatoes than Mr. T.

CASE 3.—Mrs. B., wife of mill foreman. Breakfast: Biscuits, butter and coffee; also has either eggs, chicken or fresh beef every day; is not a large eater, however; jelly or preserves.

Dinner: Salt pork with beans or cabbage, Irish potatoes; during summer has plenty of vegetables, but all winter only beans and cabbage; cornbread; milk sometimes during summer, but never in winter.

Supper: Same as dinner. For the four in the family, including two children, they purchase monthly: 50 pounds of flour, 2 pecks cornmeal, 2 pecks potatoes.

CASE 4.—Mr. P., government employee. Breakfast: Hominy, a considerable amount; ham and steak were always served, but he liked ham best and would eat that and afterwards perhaps a small piece of steak; bread, biscuits and coffee; ate from four to five biscuits every morning; pancakes and syrup often; coffee.

Dinner: Salt meat with beans, cabbage or turnips, a couple of good sized pieces of cornbread, pie or cake; seldom ate fresh meat for dinner.

Supper: Hash, cornbread and butter, also bakers' bread; ate plenty of cornbread and sometimes ate some cold vegetables.

CASE 5.—Mrs. A., sister of physician who lived with her, history obtained from Dr. A. Breakfast: Occasionally fruit and occasionally hominy; did not care much for cereals; bacon and an egg regularly, except when varied with a piece of steak or chicken; biscuits, butter and coffee; hot cakes and syrup frequently.

Dinner: Fresh meat or chicken nearly every day; Irish potatoes and a few vegetables; pie and cake, fruit; cornbread.

Supper: Cold meat, bread and preserves; stated that she was fond of bread and syrup; did not drink milk, did not care for it; stated that she was a fairly hearty meat-eater. However, there were four adults in the family, and a two-pound roast was sufficient for all for one day and sometimes part of the next. Used about a dozen eggs a week through the year.

In December she had a baby and nursed it until middle of April, when she was taken sick. Child at birth weighed 10 pounds and weighed 17 pounds when she was taken sick. Lost 20 pounds from December 10 until date of first illness. She has never been in contact with a case of pellagra so far as known.

CASE 6.—Mrs. D., housewife in comfortable circumstances. Breakfast: Grits or oatmeal, ham or bacon; eats an egg about two mornings a week; bread, biscuit and postum. States that the chief part of her breakfast is bread and butter and postum.

Dinner: Soup (canned), beans and Irish potatoes; cabbage, corn and other vegetables in summer, but all winter main part of dinner is beans and potatoes; bread and often pie or cake; one glass buttermilk.

Supper: Same as dinner.

Meat is served often, but patient states that she does not care for it and almost never eats it. Three adults in family purchase monthly: 100 pounds flour, 1 peck cornmeal, 1 peck potatoes.

CASE 7.—Mrs. B., wife of hardware dealer in comfortable circumstances. Breakfast: Hominy and other cereal; one egg nearly every morning; biscuits or toast, or batter cakes with coffee; very rarely a small piece of steak.

Dinner: Macaroni occasionally, usually Irish potatoes or rice; steak is served for the rest of the family, but she never eats it. States that she never has cared for meat. Occasionally had chicken or fish and might eat a little of these. Practically no vegetables in the winter, when she ate almost nothing but potatoes and bread. Even during the summer, when vegetables were plenty, she ate mostly potatoes, as she preferred them. Has also been a hearty bread-eater, and eats more of this than anything else. Says she could almost live on bread.

Supper: Just bread and jelly. Has eaten this for supper as long as she can remember. Did not drink milk, and used very little butter. Has continued cutting one thing after another out of her diet because she thought they caused indigestion, and for nearly a year before her illness, lived chiefly on bread and potatoes.

CASE 8.—Mrs. H., wife of well-to-do public accountant. Breakfast: Hominy with butter; hot bread and tea; during certain times of the year she ate an egg several times a week.

Dinner: Sweet potatoes or macaroni; occasionally ate a very little roast beef; several biscuits; vegetables during summer, but few in winter.

Supper: Bread and grits, tea or cocoa.

Drank very little milk, and ate almost no meat, but was a heavy bread-eater. Says she could have anything she wanted, but simply did not care for meat, eggs or milk.

It is interesting to note that the physician who treated these cases recognized the one sided nature of the diet, and placed both of these patients on a diet practically free from carbohydrates, and in each case the symptoms began to improve promptly after the change of diet.

CASE 9.—Mrs. T., housewife in well-to-do circumstances. Breakfast: Either oatmeal or grits; bacon or ham; usually ate an egg several times a week; bread, butter and coffee.

Dinner: Usually salt pork boiled with vegetables. During the winter when there were not many fresh vegetables, used canned goods. Also had canned salmon and salt fish. She served fresh beef several times a week, but she did not care for it and seldom ate it. Ate a small piece of chicken several times a week. She always had boiled rice and also Irish potatoes and ate freely of both, and also of bread. Usually had cake and stewed fruit for dessert.

Supper: Hominy with either cheese, ham or bacon, and rarely eggs. She ate a fair amount of hominy and a considerable amount of bread. States that she is a little inclined to be a vegetarian because she does not like to have animals killed. Drank no milk, ate very few eggs, and bought a large amount of canned goods.

CASE 10.—Mr. S., a freight conductor. A very large and muscular man weighing 245 pounds and apparently one of the best nourished men I have ever seen. Eruption of pellagra pronounced, but no other symptoms except that he lost fifteen pounds weight just prior to the appearance of the erythema.

Breakfast: Gets a very early start and usually eats no breakfast. When he does it consists of coffee and a biscuit.

Dinner: Almost always eats Irish potatoes fried with onions, and eats more of these than anything else; cabbage often. Does not eat meat because he does not care for it. Says he does not eat a pound of meat in six months. Has eggs perhaps once a week; beans occasionally; bread; ice cream often.

Supper: Potatoes and onions again whenever he can get them; oysters or fish occasionally, otherwise sandwiches or pie.

Stated that he might drink a glass of milk a day, and never ate butter, but that he was very fond of fresh raw eggs, and when he found some fresh ones, he might eat half a dozen at one meal. Said this did not happen more than

once or at most twice a month. Dietary habits are most erratic, as he is on the road and has to pick up what he can get a good deal of the time, but almost always orders potatoes and onions, for which he has an especial predilection.

A few other cases were seen, all of which were similar to the above. In practically every case there was some peculiarity of taste or a history of indigestion or some other circumstance as a result of which the patient had lived on a very one-sided diet, in every case consisting chiefly of flour, or corn products or potatoes, and often with the addition of salt pork in some form or of canned vegetables. Practically the only case seen in which no obvious flaw could be picked in the diet was Case 5, Mrs. A., who was the sister of a physician. In this case the patient was not seen, but the diet was obtained from her brother. But it is noteworthy that this case occurred immediately following pregnancy and a lactation, in the course of which the patient lost twenty pounds. It can hardly be asserted in view of the loss of about one sixth of the total body weight that the patient was properly nourished, even though no obvious fault can be found with her diet. Pellagra occurs very commonly in women after childbirth. The same phenomenon is seen very often in beriberi, and we may assume that if pellagra is a deficiency disease many women who are receiving sufficient vitamins in their diet to preserve them in health under ordinary circumstances succumb under the additional stress of childbearing. There is no race suicide in this part of the country, and it is quite usual to find from five to eight children in a family.

In this connection it is interesting to note that the commission finds that the incidence of pellagra is highest in women between 20 and 40 years of age; in other words during the childbearing period. The ratio between the incidence rate for female and male in each age period is as follows:

Age.....	0 to 4	5 to 9	10 to 14	15 to 19	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69
Female.....	1.1	1	0.7	..	10.8	22.1	3.5	0.5	0.4
Male.....	1.	1	1.	1.	1.	1.	1.	1.	1.

From this it will be seen that as compared with males, the incidence rate of pellagra is practically the same at all age periods for male and female except during the years of sexual activity and childbearing, when the rate is from ten to twenty times higher in women than in men. This peculiarity in distribution is readily explainable according to the dietary hypothesis, and very difficult of explanation if the disease be assumed to be an infection, and such evidence tends to make in favor the dietary deficiency hypothesis.

A number of mill villages were investigated with a view to determining whether any conclusive evidence could be obtained showing that the incidence of pellagra is directly due to the character of the

diet, that is, was more prevalent where the dietary habits were poor and less prevalent where the dietary was better, other conditions remaining the same.

Inasmuch as no conclusive evidence on this point was obtained, the discussion of the results will be much condensed. In general it was found that in those villages in which there was little pellagra, the dietary habits of the people were distinctly above the average of mill villages taken as a whole, but that the lack of pellagra could not logically be attributed to this factor alone, because in such villages the general sanitary conditions were also as a rule distinctly above the average.

The village of Newry will serve as an illustration of this point. Newry is a mill village about five miles from the town of Seneca, S. C., having a population of about 600. Cases of pellagra have moved into this village from time to time, but the disease has not spread, and there has been but one undoubted case of pellagra originating in that village.

The diet of the operatives in Newry is undoubtedly distinctly above the average of other mill villages, and the following points of superiority may be noted:

1. Fresh meat is sold all through the year. I was informed that during June, July and August, 400 pounds of fresh beef was sold weekly together with about 120 pounds of fresh fish. Many fish are also caught in a neighboring stream. Mutton is also sold during the summer, about 1,000 pounds being sold in a season. This is a distinct point of difference from most of these villages, in which no attempt is usually made to sell fresh meat during the summer. During the winter also the per capita consumption of fresh meat, fish, oysters, etc., is above that of the average mill village.

2. The manager of the village store, where practically everything consumed in the town is purchased, has made every effort to handle only the best lines of food products. Thus western cornmeal used to be sold entirely. As a result of the agitation against inferior cornmeal, however, for the past two years the best grade of western corn has been purchased and is now ground at home once or twice a week as desired. The very best quality of meal from the whole corn is therefore the only cornmeal sold at this store. The same care has been observed with regard to other food products.

3. The people of this village as a whole are economically superior to the mill villages as a whole. As a result of methods of administration, there is a very small floating population. Most of the operatives are old residents and 90 per cent. of them are in receipt of wages that may fairly be called comfortable. It may be assumed, therefore, that

in general, such people are better fed than are the operatives in villages where the per capita purchasing power is less, and where general intelligence and efficiency are distinctly less.

4. It should be noted that the only case of pellagra known to have developed in Newry was an exception to this rule, in that a family of four was supported on a wage of \$30 a month, and the diet was markedly one sided and monotonous (see Case 14, Mrs. A). The same criticisms may be made of the diets of all of the individuals who were consulted who suffered from pellagra at the time of moving into Newry.

5. In spite of the suggestive nature of this evidence, which points towards dietary deficiency, it is not conclusive because this village had from the time it was built an excellent system of water carriage disposal of wastes. This is an important exception to the average mill village, the great majority of which are provided with open privies of a more or less insanitary type. The adherent to the infection theory may therefore point to this fact as an explanation of the immunity from pellagra enjoyed by Newry.

The answer to this will probably be furnished as the result of the experience of Spartan mills, Spartanburg, S. C. Ever since pellagra has been under investigation at Spartanburg, the operatives of this mill have suffered from a very high incidence of the disease. Their diet has been that of the mill village population in general, and they have always had open privies. In the fall of 1913, however, the installation of a water carriage sewage system was commenced, and by May, 1914, toilet facilities had been finished in every house rented to operatives. The diet has remained unchanged so far as known. If pellagra fails to disappear or to be markedly reduced in amount, this will necessarily discredit the importance of proper sewage disposal as the explanation of the lack of pellagra at Newry.

It would perhaps be unfair to point to the amount of pellagra in Spartan mills this year as an evidence of failure of this sewer system to prevent the disease, since the system has only been in full operation since May of this year. It should, however, be most instructive to compare the future incidence of pellagra in this mill as compared with the incidence prior to the installation of the sewer system.

Evidence obtained at Saxon mills, Spartanburg, while not at all conclusive, in my opinion points toward dietary deficiency. In 1910 there were about 800 operatives in this mill, and the number has remained about constant since that time. In 1911 there was a very considerable increase in the amount of pellagra among these operatives, but in no year since that time has there been any very great number of cases originating. In 1910 the mills were shut down at intervals, so that beginning from July 15 they ran every other week

during the remainder of July and August. They then ran all through September and again shut down the first week in October. They have never shut down since that time. This unemployment, and the resulting shortage in per capita purchasing power may have had some influence in the diets of those who developed pellagra in the winter of 1911. This influence must have been slight, however, and there were probably other, at present unknown, factors operating which assisted in producing the epidemic in 1911. But it is interesting to note that the physician and other authorities at these mills were convinced that the disease was of dietary origin, their theory being that it was caused by bad cornmeal. Thus, prior to 1911 they were using any kind of cornmeal and much of it was bad. They made a change in 1911, and since that time have brought only locally grown corn, which is ground in local mills. The doctor also stated that he had suggested to all his patients that the use of canned goods be discontinued, and that he has endeavored to give instruction on the importance of a more evenly balanced ration, and has, therefore, advocated the use of more meat, eggs, milk, and other protein foods.

The testimony was almost unanimous to the effect that the vegetable gardens had been steadily growing better and better during the last three or four years, except for this last season, when the gardens were all poor, owing to the prolonged dry weather. The people are encouraged to have gardens.

I believe it would be impossible to shake these men from the conviction that pellagra was reduced in incidence as the result of such dietary changes. While of course this is not proof, it appears to me to be significant, especially in view of the fact that no particular sanitary improvements have been made since 1911. They still use the pail system of disposal of excreta. The superintendent of the mill stated that they were always trying to improve the condition of their operatives, and that there had been a gradual improvement in all sanitary arrangements during the last few years, but that no specific sanitary improvement had been undertaken.

I was informed that at Greensboro, N. C., there was a group of mills that were generally speaking markedly superior to the mills already visited in South Carolina, and that the diet of the operatives in particular was very liberal, but that in spite of this fact pellagra had been markedly on the increase there during the past year. These mills were accordingly visited, and the facts were found to be as stated. There are three mills, all under the same management, but having three corresponding mill villages. In all three villages there was an air of prosperity, cleanliness and general well-being far superior to the conditions found in most of the other mill villages seen. The diet in particular was in general excellent. There were several meat mar-

kets in operation the year around, a cold storage plant, and an excellent store. The quantities of meats and other foods sold were investigated and found to be above the average. It may be admitted, therefore, that the diet of these people is, as a general rule, above the average. It was also found that in previous years they had supposed there were not more than four or five cases of pellagra among the total population of these villages, which amounts to about 7,000, but that during this year they had had thirty cases. The managers of these mills, however, are quite benevolently inclined, and this past year have, on their own initiative, employed three trained nurses to visit these employees, care for the sick, and have general supervision over their hygienic surroundings. The head nurse makes periodic reports to the superintendent of all deaths, births and diseases found in these villages. Thus, this year is the first time that any definite information has been obtainable with regard to the diseases in these three mill villages. It seems to me quite possible that the recent increase in pellagra in these villages is therefore only apparent, being caused by the fact that these cases are now being reported, whereas formerly they were unnoticed.

As many as possible of the pellagrins in these villages were visited for the purpose of investigating their dietaries. As in other villages, most of the cases were found to be among the poorer people, but there was a fair number of well-to-do families in which a case of pellagra had occurred. In the great majority of cases, however, the diet of the pellagrin was found to be distinctly monotonous and one sided.

A single instance will suffice here :

Miss F., daughter of a well-to-do mill operative, has had pellagra five years. Breakfast: Biscuits, butter and jelly, coffee; salt meat, a very small quantity several times a week. Family had fresh meat several times a week but she did not care for it. Sometimes ate an egg in the morning. States that for five years she has eaten very little breakfast and sometimes does not eat more than two mouthfuls before she goes to work. She is often not even hungry for her dinner.

Dinner: String beans, or other vegetables, with biscuits or cornbread. In the winter there are few vegetables and she eats beans and Irish potatoes; never eats meat.

Supper: Same as dinner.

Is a hearty bread-eater when she does eat; wheat bread mostly used; drinks no milk; has fruit in summer time.

A comparative study of the diet and general sanitary condition of two institutions was made. The county home at Spartanburg is a charitable institution maintained by the county for its poor and is in reality a large farm. There has been but one undoubted case of pellagra originating on this farm. The inmates live in a little group of cottages in fair sanitary condition. Privies are used except in the hospital. This hospital is a cottage like the others, about 100 yards

from the main group of buildings. It is at present used entirely for poor pellagrins, and a considerable number of cases have been sent there this summer. Although these patients for the most part remain in the hospital, there is no strict segregation practiced, and contact with the other inmates probably has been frequent. All the buildings are unscreened except the hospital, which is partly screened. It was full of flies, however, which could easily pass from the hospital to the kitchen, which was the building nearest to the hospital, or to the other buildings. Yet the disease has not spread among the other inmates of the home.

The diet of the inmates of this home, while not luxurious, is undoubtedly superior to what they had received at their own homes, or to the average diet of the mill village population. Its main points of superiority lie in the fact that the farm has a large herd of cows, as a result of which the supply of milk is practically unlimited, and in the fact that there is a fairly liberal supply of fresh meat. A very large vegetable garden also supplies a sufficiency of all fresh vegetables in season. In general the diet is as follows:

Breakfast: Rice, hominy or oatmeal; bacon or canned salmon; eggs twice a week; bread, butter and molasses; coffee and milk.

Dinner: During the summer, fresh beef or chicken are served on alternate Sundays. During the winter fresh meat is served every day, either beef or pork. Irish potatoes and an ample supply of fresh vegetables are supplied.

Supper: Cornbread, milk and molasses, with the remains of the dinner. A pitcher of milk is always on the table, and all drink as much as they desire. It was stated that many drank two quarts daily.

The Thornwell Orphanage, Clinton, S. C., is a most excellent institution, caring for about 300 orphans. For several years it has been a hotbed of pellagra. The institution has beautiful grounds with substantial stone pavilions, each accommodating a matron and about twenty children from 5 to 18 years of age. There are separate pavilions for boys and girls. Each pavilion has a water closet, but the water supply is insufficient, so that they often cannot be used. At such times open privies are used, and as the children are not very closely supervised, they are distinctly insanitary and much is left to be desired in this respect.

THE TOTAL DAILY DIET FOR 137 CHILDREN

The diet also is very monotonous and one sided. The meals are all cooked at a central kitchen. At the time of our visit there were only 137 children in the home, and the following gives the actual diet of these children as shown on the record book of the kitchen from August 1 to 5 and 10 to 17, the total daily diet for 137 children:

August 1: 5 gallons skimmed milk; 40 pounds flour; 16 pounds lard; beans and corn, amount not stated; 9 cans tomatoes; 4 cans oatmeal—1.5 pound cans; 36 loaves bread.

August 2: 5 gallons skimmed milk; 40 pounds flour; 13 pounds lard; 70 pounds ham; 56 loaves bread; corn; 3 pounds butter; 4 cans oatmeal.

August 3: 5 gallons skimmed milk; 40 pounds flour; 15 pounds lard; beans; corn; 10.5 pounds bacon; 4 cans oatmeal; 36 loaves bread; one-half case fish roe, canned.

August 4: 5 gallons separated milk; 40 pounds flour; 15 pounds lard; 4 cans oatmeal; beans; 15 pounds bacon; corn; 40 loaves bread; 100 pounds rice; 30 eggs; 7.5 pounds sugar.

August 5: 4 gallons separated milk; 31 pounds flour; 10 pounds bacon; 9 pounds rice; 6 pounds lard; 4 cans oatmeal; 3.25 pounds bacon; beans; tomatoes; 36 loaves bread.

August 11: biscuits, oatmeal, beans, eggs boiled, rolls.

August 12: oatmeal, biscuit, corn, soup of 5 pounds bacon, rolls.

August 13: biscuit, three times; oatmeal, beans, beef, rice, rolls.

August 14: biscuit, oatmeal, beef, rice, corn, boiled; rolls.

August 15: biscuit, oatmeal, soup, rolls, tomatoes, raw; figs.

August 16: biscuit, oatmeal, ham, corn, stewed; tomatoes, stewed; rice bread.

August 17: biscuit, oatmeal, corn; stewed; pilau of rice and ham, rolls, ginger bread.

This is a fair sample of the summer diet of the institution. No meat has been served all summer. In the winter they have ham or chicken on Sundays, beef on Wednesdays and Saturdays, and beans on the other days. The supply of fresh vegetables is small in the winter. Syrup is served three times a day and I was informed that the majority of the children eat biscuits and syrup as the main part of the meal.

It is apparent that the main part of the diet of these children consists of wheat flour. The protein constituents are at all times too low, and during the winter, while there is a little more meat, the vegetable supply is markedly reduced. On account of the insanitary condition of the privies it is not possible to incriminate the diet alone as the cause of the incidence of pellagra in this institution, but it seems to me that this obvious defect may very well be the cause.

It may be said, however, that these two institutions afford some evidence in favor of the dietary deficiency hypothesis, and no evidence that disproves this theory. This is the end-result of all of the observations, and we may therefore conclude that no evidence has been found that directly disproves the dietary deficiency theory, but that, on the other hand, there are a number of points in these observations that tend to confirm this theory.

CHANGES OCCURRING DURING THE LAST TEN YEARS THAT MAY ACCOUNT FOR THE INCREASE IN PELLAGRA

It is undoubtedly true that pellagra has existed in this country for some time. Physicians who have been many years in practice state that twenty years ago they had cases in their practice that they then diagnosed in various ways, such as intestinal tuberculosis, but that they now know were cases of pellagra. It is possible and even probable that there was considerably more pellagra then than is generally supposed,

since no one was thinking of that disease. Now that attention is focussed on pellagra, many cases are being diagnosed that suffer from the disease in a very mild form, perhaps suffering only from the typical erythema and totally lacking other symptoms. Such cases would undoubtedly have been very generally overlooked twenty years ago. But while it seems possible, therefore, that the recent increase in the incidence of pellagra may to some extent be explained in this way, it is also apparent that it is becoming more common throughout the South from year to year. This may be regarded as an undoubted fact, and if pellagra is due to a dietary deficiency, it is clear that some explanation must be offered to account for the great increase of pellagra in recent years in accordance with this hypothesis. An attempt was accordingly made to discover any facts that would indicate that changes have occurred in the dietary of the population as a whole during the last ten years, and the information obtained may be discussed as follows:

1. Changes in the population itself: Spartanburg county was selected because of the great increase in the amount of pellagra occurring in this county. The total population of Spartanburg County for the last three decades, according to the U. S. Census, was as follows:

1890.....	55,385
1900.....	65,560
1910.....	83,465

The total population of Spartanburg township, which includes the city of Spartanburg, during the same years was as follows:

1890.....	13,616
1900.....	23,810
1910.....	31,354

It will be seen that there has been a great increase in the population of Spartanburg County during the last twenty years, and particularly of Spartanburg Township, which is almost three times as great as in 1890. Such a large increase is quite unusual for the South and shows a marked variation as compared with the total population of the whole of the state of South Carolina, which was as follows for the same years:

1890.....	1,151,149
1900.....	1,340,316
1910.....	1,515,400

The increase over the preceding census was as follows:

1890.....	155,572
1900.....	189,167
1910.....	175,084

The percentage of increase as compared with the percentage of increase of the whole United States is as follows:

	S. C.	U. S.
1890.....	15.6	25.5
1900.....	16.4	20.7
1910.....	13.1	21.0

From these figures it will be seen that the total population of Spartanburg County, and particularly Spartanburg Township, has increased enormously as compared with the increase in the population of the whole state, in which the increase was in all years considerably below the rate of increase for the United States as a whole.

This increase is to be attributed to a change in economic conditions. It is during these years that most of the large cotton mills have been established in this country, and the increase is largely attributable to the influx of mill operatives and the increased business produced by these mills. It will thus be seen that economic conditions have been completely changed in this country during the last twenty years. While I have had no time to collect statistics from other parts of the South, it is generally recognized that similar changes have been occurring in many localities, and as a whole, the entire South has turned more largely to industrial, manufacturing and mining operations than was the case twenty years ago. In many places, therefore, communities have changed from agricultural pursuits to industrial pursuits, and experience has shown that it is these industrial workers who are especially prone to develop pellagra. Thus the incidence in the mill villages population of Spartanburg County is 104 per 10,000 against 19 per 10,000 for the remainder of the county. Such changes may reasonably explain a great part of the recent increase in pellagra, and when it is admitted, as I believe is the fact, that the dietary of the mill village population as a whole is distinctly inferior to that of the remainder of the people in the county, the possible relation of diet to the increase in pellagra becomes apparent.

2. Changes in the purchasing power of the population during the last decade is important. It is extremely difficult to obtain any definite information on this point, but the testimony is general that economic conditions are generally better in the South now than they were ten years ago. There has been more money in circulation. The price of crops, and particularly of the cotton crop, has as a general rule steadily increased. The people as a whole are making more money. In the case of the mill operatives themselves, although there has been very little increase in the rate of wages, competition between mills has forced an increase in the efficiency of the workers, so that where a weaver ten years ago possibly tended ten machines, he now tends twenty. Although the price per piece may have remained the same, as he now produces much more cloth, he naturally receives a proportionate increase in wages.

But at the same time the purchase price of most commodities, and particularly of the foodstuffs, has soared. Thus, I was informed by one storekeeper, that ten years ago he sold three pounds of his best steak for 25 cents, whereas now the price of steak is 17½ cents a

pound. In other words, the price of beef here is more than double the price ten years ago. Ten years ago he sold eggs at three dozen for 25 cents; now they are 20 cents a dozen, or almost three times the former price. It is unnecessary to dilate further on this tendency for the prices of food to rise, for it is felt and generally recognized all over the country. It is an open question whether the increase in wages in the South has kept pace with the increased price of food, and it seems quite possible that an increasing portion of the population find it more and more difficult to purchase fresh meat, eggs, vegetables and fruits, and that there is accordingly a tendency for many people to cut down the consumption of these high-priced articles of food and increase the consumption of such staples as cornmeal, hominy and flour.

3. An attempt was made to determine whether such changes could be actually demonstrated. Inquiry as to the consumption of fresh meat was made. I was informed by several physicians who had been in practice many years in Spartanburg County that they were certain that as a general rule less fresh meat is eaten now than was the case ten years ago, this fact of course being due to the great increase in the cost of meat. There is practically no meat shipped into Spartanburg County by the western packers, and even in the city of Spartanburg there are no cold storage facilities. All animals consumed are killed locally and promptly consumed. It is largely because of this fact that so little meat is used in the dietary during the summer. On investigation it was found that almost the entire wholesale meat business in Spartanburg County was controlled by one man, Mr. L. S. Donahoe, who operates a slaughter house on the outskirts of Spartanburg. Mr. Donahoe was accordingly visited and he informed me that he was selling just about the same amount of meat to Spartanburg now as formerly; that his business had increased considerably, but that this increase was due to the fact that he was selling meat in other counties, whereas formerly his business had been confined to Spartanburg County. He assured me that he knew to a beef just how much meat had been furnished every year for the past ten years and that the amount remained practically constant for each year. He also promised to give me the exact figures covering the number of animals slaughtered and sold to Spartanburg County for each year, but repeated requests have failed to elicit these important statistics. However, if Mr. Donahoe's statement is accepted at its face value, it is certain that the per capita consumption of fresh meat is much less now than it was ten years ago, for he is now selling about the same amount of meat to a population of 83,465 that he formerly sold to a population of 65,560, according to the preceding census figures.

As to the consumption of canned goods, on every hand testimony was obtained indicating a constant increase. The firm of Shockley and Bull is probably the largest wholesale dealer in such supplies in Spartanburg, and Mr. Shockley was so obliging as to personally compile the following statistics.

Canned goods sold by Shockley and Bull during the fiscal years, 1909 to 1913:

	Canned Meats, Dozen Cans, 1 lb. Basis	Canned Vegetables, Dozen Cans, 3 lb. Basis	Canned Fruits, Dozen Cans, 2½ lb. Basis
1909.....	4,060	5,630	822
1910.....	8,091	4,625	328
1911.....	9,301	4,312	199
1912.....	7,687	4,509	540
1913.....	12,218	7,715	532

Mr. Ashmead Courtenay also very kindly sent me the following figures indicating the sales of canned goods at the company store at Newry, S. C.

	Meat, Dozen Cans	Fish, Dozen Cans	Vegetables, Dozen Cans
1906.....	276	325	228
1907.....	469	351	418
1908.....	244	392	356
1909.....	121	324	518
1910.....	160	455	370
1911.....	307	285	294
1912.....	247	274	385
1913.....	332	283	478
1914.....	404	297	614

Similar figures and statements were obtained from all that were questioned on the subject. The facts appear to be that there has been considerable fluctuation in the amounts of canned goods consumed from year to year. Thus, in a year when the gardens are poor, more canned goods are used. But on the whole, there is a well-defined increase in the amount of canned goods used at present over the amount used ten years ago.

The possible changes in the kind of cornmeal and flour used was also investigated. It was found that changes in the variety and quality of both cornmeal and flour used have been frequent. For many years corn has been under consideration as a cause of pellagra, and it is very common to find that as a result of the occurrence of pellagra certain people have eliminated corn from the diet, or have used a locally ground corn in place of shipped cornmeal. Practically all of this cornmeal, however, is made from the whole corn and is not decorticated. On the other hand, practically all of the flour used is fine white flour that has been deprived of all of the outer coats of the

grain, and must therefore be considered deficient in vitamins. But no evidence was obtained indicating any changes in these staples that could account for the increase in pellagra in recent years.¹³ It seems more probable that if pellagra is caused by a dietary deficiency, this deficiency has always existed in the cornmeal and flour used, and that the recent increase in the disease is caused by a relatively increased consumption of these articles, with a relative decrease in the consumption of other and more expensive foods.

While endeavoring to elicit information as to changes in the food habits of the people, I was struck by the large number of cases in which information was volunteered as to the change in the lard used. It appears that ten or fifteen years ago about nine tenths of the lard used was pure leaf lard from the hog. Since that time various firms have marketed cottonseed oil substitutes for lard, or compound lards containing a considerable portion of cottonseed oil mixed with lard. The latter, of course, is considerably cheaper. Thus, one store informed me that in 1907 they sold more pure lard than compound, while now they sell ten times as much compound lard as leaf lard. A few people even hazarded the opinion that pellagra might be due to the use of cottonseed oil. As popular opinion at times incriminates about every article of food used, such opinions are worthless. However, it may be pointed out that we know very little of the food value of cottonseed oil as compared with lard, and it is quite possible that lard may be more readily assimilated and may possess a higher food value than cottonseed oil. Further, such a marked change in the dietary habits of a community is a sufficient refutation of the argument that pellagra can not be of dietary origin, because there has been no change in the food habits of the people. Such changes have occurred. The changes mentioned may or may not be important in the causation of pellagra. But even if these changes are unimportant, the fact that they can be demonstrated opens the possibility that there may be other and more important changes that may have occurred in the food habits of the people during the last decades, and that some of these changes may be connected with the contemporaneous increase in the incidence of pellagra.

In conclusion it may be stated with regard to the foregoing argument that while I have endeavored to avoid making unfair statements or comparisons, I have made no attempt to present arguments in favor of the infection or intoxication hypotheses. The commission requested that I attempt to present the case for the dietary hypothesis as I see

13. Voegtlin, Sullivan and Myers, *Pub. Health Rep.*, April 14, 1916, p. 935, stated that this highly milled wheat flour began to be introduced about 1880. If this statement is correct, the introduction of this foodstuff, proved to be deficient in vitamins, corresponds closely with the increase in pellagra.

it, and I have endeavored to do this, knowing that the presentation of the other side would be left in competent hands. While I am personally inclined to believe that the most probable cause of pellagra is a deficiency in some vitamin, it is evident that this hypothesis has not been scientifically demonstrated, but is still only hypothesis. It is believed, however, that the following conclusions may be drawn from this investigation.

CONCLUSIONS

1. There is a certain similarity between pellagra and other known deficiency diseases, namely, beriberi and scurvy.

2. Much of the evidence that has been presented as a proof of the infectious nature of pellagra can be reasonably explained in accordance with a deficiency hypothesis.

3. A deficiency is demonstrable in the diets of most pellagrins. This deficiency appears to me to result from the too exclusive use of wheat flour, in association with cornmeal, salt meats and canned goods, foods that are known to be deficient in vitamins.

4. Changes in the diet of the people of the South have occurred during the past ten or fifteen years. Since we do not know all the changes that have occurred, and cannot judge accurately the importance of the known changes, it is unscientific to assume that the recent increase in pellagra cannot be due to such changes.

5. The hypothesis that pellagra is caused by a deficiency is very plausible and must be taken into consideration in subsequent studies of this disease.

THE INCIDENCE OF PELLAGRA IN SPARTANBURG COUNTY, S. C., AND THE RELATION OF THE INITIAL ATTACK TO RACE, SEX AND AGE*

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INTRODUCTION

The extensive records accumulated during the field study of pellagra in Spartanburg County, S. C., have presented an opportunity to inquire into the behavior of this disease in a population of considerable size living under natural conditions of civil life. Such an inquiry might be expected to contribute something to the general prognosis of pellagra in the population of the county and in the Southern states as a whole and it might even bring to light some facts of value in the prognosis in an individual case of the disease. Manifestly, also, it is desirable to know fairly well the course of the disease as a biological phenomenon, uninfluenced by intentional drugging, dieting or climatic changes, in order to estimate the possible influence which these latter may exert on the course of pellagra. Fortunately for the purpose of such a study, a considerable proportion of the pellagrins of our series have received no particular treatment directed against the disease; in fact, many had suffered from pellagra for years without the nature of the ailment being recognized. The recorded material is rich in possibilities of analysis. It seems wisest to direct attention to certain specific points, one at a time. Many important facts in regard to these cases will be found recorded and discussed in other papers of this series, constituting our third report, and also in the preceding first and second progress reports of this commission.

In the present paper we purpose to present the recorded facts in respect to incidence of pellagra and its death rate in the year of initial attack in each year since the appearance of the earliest recognized case in the county and the correlations between race, sex and age on the

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* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* The final copy of this paper has been written since Dr. Garrison and Dr. Siler were recalled to active duty in the Medical Corps, U. S. Navy, and the Medical Corps, U. S. Army, respectively. Although they are quite familiar with the general nature of the paper and with the conclusions, they are not personally responsible for the detailed compilation of data or for the specific deductions drawn from them.

one hand, and incidence of pellagra and death rate in initial attack on the other, as shown by the total cases on our records at the end of the field work in 1914. In subsequent papers we purpose to consider the tendency to recurrence, death rate in recurrence and tendency to recovery.

The present paper deals only with incident, or initial attacks, of pellagra and not with recurrences of the disease, a sharp distinction being made between incident, or first attack, and subsequent, or recurrent attack, of the disease.

INCIDENCE OF PELLAGRA IN EACH YEAR

In all cases of our series subsequent to 1907, we have arrived at a decision concerning the year in which the first erythema appeared, but we do not wish to maintain that these decisions are in every case correct. For those cases originating previous to 1908 it has not been possible to arrive at a decision in all instances. Of the 1,180 recognized pellagrins on our records at the end of 1914, there are fifty-seven cases in which the initial erythema appeared before 1908. The available evidence indicates with considerable certainty that the initial attacks appeared in these patients in the different years as shown in Table 1.

TABLE 1.—DISTRIBUTION OF CASES OF PELLAGRA INCIDENT BEFORE 1908, ACCORDING TO YEAR OF ONSET OF THE FIRST ERYTHEMA

Year.....	1888	1889	1890	1891	1892	1893	1894	1895	1896	1897	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	Uncertain	Total
Patients.	1	0	0	0	1	1	2	0	0	0	1	0	3	3	2	6	5	10	6	14	2	57

Concerning those pellagrins who suffered their first attack in 1908, 1909, 1910 or 1911, we have somewhat more reliable information, because during these years the physicians of the county were already acquainted with the disease, but it is still probable that the list of cases is very far from complete, more particularly in the earlier years. The recorded statistics for 1912, 1913 and 1914, and probably also for 1911, are distinctly more reliable and complete and probably approach very nearly the degree of accuracy attainable in field work of this sort, because of our presence in the field during 1912, 1913 and 1914. We are inclined to regard the recorded statistics for 1912 as somewhat more complete than those for 1914, because the observations made in 1912 have been added to by further observations during two subsequent years. The incidence of pellagra in each year subsequent to 1907 is shown in Table 2 and the data are presented graphically in Figure 1.

TABLE 2.—DISTRIBUTION OF TOTAL RECORDED PELLAGRINS ACCORDING TO YEAR OF ONSET OF FIRST ERYTHEMA

Year.....	Before 1908	1908	1909	1910	1911	1912	1913	1914	Total
Patients.....	57	20	57	141	234	211	251	209	1,180

The recorded data indicate that the number of new cases each year has increased rapidly from 1908 to 1911, and that the incidence rate has changed but little from 1911 to 1914. These indications may be questioned to some extent. We are inclined to accept the indication of an actual rapid increase from 1908 to 1911 in the number of individuals newly attacked by pellagra, but we think that the magnitude

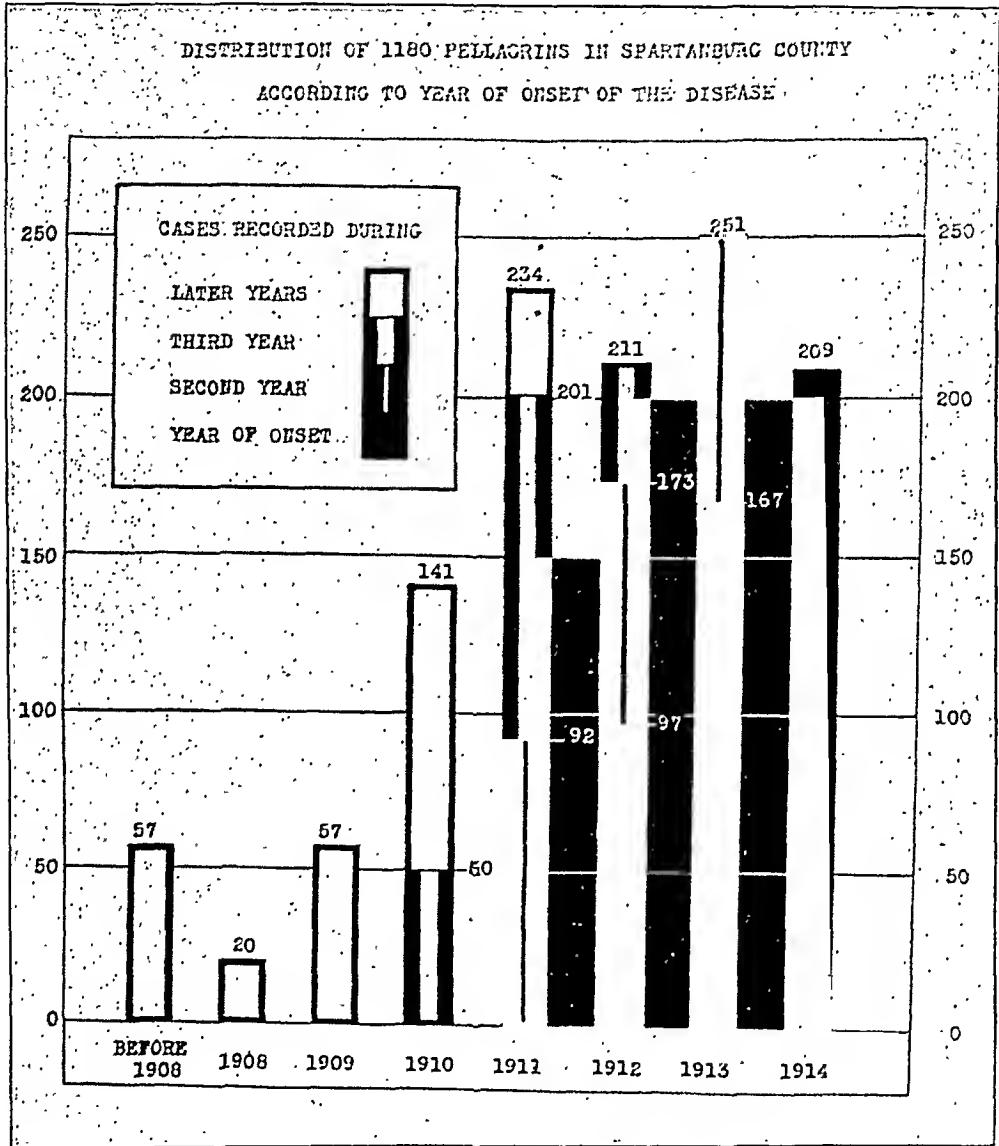


Fig. 1.—The total height of each column indicates the total number of new cases of pellagra in the respective year, according to our records at the end of 1914. The height of the solid black column indicates the number of new cases recognized and recorded by us during the year in which the disease began. For 1914 the whole column is, of course, solid black.

of this increase is somewhat exaggerated in the table because of relatively incomplete records for the earlier years. In other words, we are actually convinced that there were very many more new cases of pellagra in Spartanburg County in 1911 than in 1908, probably at least

four times as many, but the indicated elevenfold increase appears too large. In the statistics of cases originating subsequent to 1911 another factor of error assumes prominence. This depends in part on the evident tendency of many pellagrins to conceal their disease until it recurs once or even twice, and in part on the necessary incompleteness of our survey of the county in each year, as a result of which many incident cases, especially those arising later in the season, escaped discovery during the year of the initial attack. Thus, at the end of 1912, our first year in the field, we had recorded only ninety-two cases which originated in 1911; at the end of 1913 this number had been augmented to 201, and at the end of 1914 it had been further increased to a total of 234. In a similar way the number of pellagrins with onset in 1912 who had been recognized and recorded at the end of 1912 was only ninety-seven; in 1913 there were added seventy-six, making 173, and during 1914 there were discovered thirty-eight more pellagrins with onset in 1912, augmenting the total to 211. The number of patients with onset in 1913 recognized and recorded during 1913 was 167, and in 1914 we added eighty-four to this number, making a total of 251 with initial attack in 1913. If, therefore, one should compare the total recorded pellagrins incident in 1914 with the analogous figures for 1912 and 1913, as the figures stood at the end of the field work of the respective years, a very considerable increase in the new cases of pellagra would be indicated, namely, from 97 to 167 to 209 for 1912, 1913 and 1914, respectively. We are not inclined to regard these figures as a true measure of the increase in new cases of the disease in the last few years, for it is doubtless true that the data obtained in 1914 are more complete than those obtained in previous years, because of the greater experience of the observers and more thorough acquaintance with the field of work, but in this connection it should be mentioned that our field work ended on Oct. 15, 1914, and necessarily many portions of the county had not been visited for several weeks previous to that time. Judging from the experience of earlier years, it seems assured that further systematic field work in 1915 and 1916 would bring to light from sixty to eighty additional cases of pellagra which had their onset in 1914.

The year 1911 merits special consideration because of the relatively excessive number of pellagrins recorded as having the initial attack in that year. It is possible that some cases which actually originated earlier have been placed in 1911, because of the widely awakened interest in pellagra in Spartanburg County during this year. Dr. R. M. Grimm¹ made an epidemiologic survey of certain portions of this county in 1911, and there can be no doubt but that his presence and the

1. Grimm, R. M.: Pellagra: a Report on Its Epidemiology, U. S. Pub. Health Rep., 1913, xxviii, 427, 491.

stimulus of his work brought to light many cases not previously recognized, although the disease had actually originated earlier in these patients. On the other hand, many physicians who have been practicing in the region for many years have expressed the opinion that 1911 was an exceptional year for pellagra and that a disproportionately large number of new cases actually did arise in that year, not only in many parts of Spartanburg County, but also in neighboring counties. This opinion possesses some weight and lends support to the indication of high incidence in 1911 shown by the recorded statistics.

From a consideration of these various sides of the question, we have arrived at the conclusion that the number of new cases of pellagra in Spartanburg County has been increasing somewhat, probably about 10 per cent. per year on the average, during the last three or four years, and that the increase previous to 1911 was at a more rapid rate.

DEATHS DURING THE YEAR OF INITIAL ATTACK

For the purpose of this study we have arbitrarily decided to consider a death which occurred previous to February 1 of the year following the initial erythema as a death in the first attack of pellagra. In many instances it has been impossible for us to estimate the relative importance as a cause of death of the pellagra as compared with other diseases from which the patient may have been suffering, and therefore unless it has been perfectly clear that death resulted without relation to pellagra the death has been included as due to this disease.

Of the total 1,180 recorded pellagrins, 187 died during the year of initial attack, as defined in the preceding paragraph, indicating a death rate in the first attack amounting to 15.8 per cent. This figure is undoubtedly too high rather than too low, because in pellagra, as for vital statistics in general, mortality reports tend to be more complete than morbidity reports, however much care be devoted to the matter. Doubtless, also, some of these deaths occurred during a year subsequent to that of the initial erythema, the latter having escaped observation and record.

The deaths in initial attack include, as previously stated, those deaths which occurred up to February 1 following the year of initial erythema, in addition to those which occurred in the respective year. Their distribution by years is shown in Table 3.

TABLE 3.—DISTRIBUTION OF DEATHS IN INITIAL ATTACK OF PELLAGRA
ACCORDING TO YEAR OF ONSET OF THE INITIAL ERYTHEMA

Year.....	Before 1908	1908	1909	1910	1911	1912	1913	1914	Total
Incident cases.....	57	20	57	141	234	211	251	209	1,180
Deaths.....	13	2	16	28	33	27	38	30	187
Death rate, per cent.	22.8	10.0	28.1	19.9	14.1	12.8	15.1	14.4	15.8

The gross indicated death rate, 15.8 per cent., is after all not so very much greater than the rate calculated for each of the last four years. One may conclude, therefore, that the death rate for pellagra in Spartanburg County has been between 10 and 16 per cent., and that there is no conclusive evidence that this death rate has increased or diminished progressively during the past four years. Previous to 1911 the death rate indicated by the records was considerably higher, but this indication should not be too readily accepted without some thought of the incompleteness of the data. It is not improbable that an appreciable number of those who died of pellagra in 1909 and 1910 may actually have had an unrecorded initial erythema in some previous year, so that they really died in a recurrence rather than in the first year of the disease.

RELATION OF PELLAGRA INCIDENCE TO RACE, SEX AND AGE

The important relations of age and sex to pellagra, as well as the racial distribution of the disease, have been discussed in our previous reports, more completely in the second progress report.² It is our purpose to consider these relationships in greater detail in the much larger group of cases now available.

Of the total 1,180 recorded pellagrins, 1,026 were white and 153 were colored (including mixed blood), giving a ratio of 6.7 to 1. This agrees well with the ratio shown in the previous report, cited above, upon the 780 cases recorded to the end of 1913, of which 680 were white and 100 colored, giving a ratio of 6.8 to 1. The number of white persons and colored persons who suffered an initial attack of pellagra in each year subsequent to 1907 is indicated in Table 4. According to the available records the proportion of negro pellagrins was relatively less some years ago and has been increasing somewhat since 1911. Of the 509 recorded initial attacks up to the end of 1911, there were fifty-three, or 10.4 per cent., in colored persons, whereas, of the 671 cases originating since the end of 1911, no less than 100, or 14.9 per cent., have been in the colored race.

TABLE 4.—WHITE AND COLORED PELLAGRINS DISTRIBUTED ACCORDING TO THE YEAR OF INITIAL ERYTHEMA

Year.....	Before 1908	1908	1909	1910	1911	1912	1913	1914	Total
White.....	51	20	53	123	209	182	213	176	1,027
Colored.....	6	0	4	18	25	29	38	33	153
Total.....	57	20	57	141	234	211	251	209	1,180
White, per cent.	89.5	100.0	93.0	87.2	89.3	86.3	84.9	84.2	87.9
Colored, per cent. ...	10.5	0.0	7.0	12.8	10.7	13.7	15.1	15.8	13.0

2. Siler, Garrison and MacNeal: Statistics of Pellagra in Spartanburg County, S. C., *THE ARCHIVES INT. MED.*, 1915, xv, 98; Second Progress Report, 1915, 121.

In our previous report it has been pointed out that the white population of Spartanburg County is about twice as numerous as the colored population, 57,048 and 26,410, respectively, according to the U. S. Census, 1910, so that the pellagra morbidity among negroes was only about one third of the morbidity rate for the white population. As we have previously stated, we regard this disparity not as evidence of racial resistance to pellagra on the part of negroes, but as a result of their different living conditions and partial social segregation from the inhabitants of the endemic foci of the disease. It now appears that this disparity is showing a slight tendency to become equalized, but that the negro race still remains very much less afflicted with pellagra than the white race in Spartanburg County. The gradual relative increase of pellagra in the colored race in this county might be expected as the disease gradually extends more and more from its principal endemic foci in the mill villages out into the rural population.

The relationship between race and death rate from pellagra clearly indicates lesser resistance in the negro race, once the disease has been contracted. Of the 1,027 white pellagrins, 123, or 12 per cent., died in the year of the initial erythema (including the following January), whereas, of the 153 negro pellagrins, no less than sixty-four, or 41.8 per cent., died during the year of the initial erythema. In short, pellagra in Spartanburg County attacks members of the negro race less frequently, but it is far more fatal to them when they are attacked, a condition of affairs which finds analogy in many other diseases due to infection.

The high death rate in pellagra among negroes in the United States has been repeatedly observed. Searcy's early report³ indicated a high death rate among negroes in a hospital for the insane, namely, 64 per cent. Lavinder⁴ has published the statistics of reported cases and reported deaths in Mississippi from January to June, 1913. The ratio between number of reported deaths and number of reported cases in the white race was 74 to 648, or 11.4 per cent., and the analogous ratio for the negro race was 194 to 665, or 29.2 per cent.

The relationship between age and sex and the incidence of pellagra has been discussed in our previous reports. In the series of 1,180 cases now available, the relationships are similar in character to those previously found, but the larger number of cases now warrants the consideration of these questions in somewhat greater detail. In the present study each case has been tabulated according to age at onset of the initial erythema and the data are shown in Table 5. The distribution,

3. Searcy, George H.: An Epidemic of Acute Pellagra, Jour. Am. Med. Assn., 1907, xlix, 37.

4. Lavinder, C. H.: Pellagra in Mississippi, U. S. Pub. Health Rep., 1913, xxviii, 2035.

TABLE 5.—DISTRIBUTION OF PELLAGRINS ACCORDING TO RACE, SEX AND AGE
AT ONSET OF FIRST ERYTHEMA

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0.....	1	2	3	0	0	0	1	2	3
1.....	4	6	10	0	1	1	4	7	11
2.....	7	12	20*	0	0	0	7	12	20*
3.....	12	8	20	0	0	0	12	8	20
4.....	17	14	31	0	1	1	17	15	32
5.....	6	8	14	0	1	1	6	9	15
6.....	11	19	30	1	0	1	12	19	31
7.....	11	9	20	0	1	1	11	10	21
8.....	9	5	14	0	0	0	9	5	14
9.....	10	8	18	1	2	3	11	10	21
10.....	7	8	15	0	0	0	7	8	15
11.....	4	5	9	0	0	0	4	5	9
12.....	2	2	4	0	0	0	2	2	4
13.....	4	1	5	0	0	0	4	1	5
14.....	1	6	7	0	0	0	1	6	7
15.....	2	2	4	1	0	1	3	2	5
16.....	8	0	8	3	0	3	11	0	11
17.....	12	3	15	3	1	4	15	4	19
18.....	13	2	15	5	1	6	18	3	21
19.....	12	1	13	4	0	4	16	1	17
20.....	15	0	15	1	0	1	16	0	16
21.....	20	3	23	5	2	7	25	5	30
22.....	23	4	27	6	2	8	29	6	35
23.....	25	2	27	8	0	8	33	2	35
24.....	23	1	24	7	0	7	30	1	31
25.....	31	5	36	6	1	7	37	6	43
26.....	26	3	29	2	0	2	28	3	31
27.....	20	1	21	2	0	2	22	1	23
28.....	14	3	17	2	1	3	16	4	20
29.....	20	2	22	3	0	3	23	2	25
30.....	22	1	23	9	1	10	31	2	33
31.....	19	1	20	2	0	2	21	1	22
32.....	19	6	25	3	0	3	22	6	28
33.....	20	3	23	3	1	4	23	4	27
34.....	22	6	28	4	0	4	26	6	32
35.....	22	4	26	2	1	3	24	5	29
36.....	14	7	21	4	1	5	18	8	26
37.....	15	9	24	1	1	2	16	10	26
38.....	9	1	10	0	1	1	9	2	11
39.....	12	2	14	2	0	2	14	2	16
40.....	14	7	21	2	0	2	16	7	23
41.....	7	3	10	1	0	1	8	3	11
42.....	18	5	23	1	0	1	19	5	24
43.....	7	4	11	0	0	0	7	4	11
44.....	12	6	18	1	0	1	13	6	19
45.....	6	4	10	2	1	3	8	5	13
46.....	9	3	12	2	0	2	11	3	14
47.....	4	4	8	0	0	0	4	4	8
48.....	5	3	8	0	1	1	5	4	9
49.....	5	5	10	2	0	2	7	5	12
50.....	7	4	11	3	3	6	10	7	17
51.....	7	4	11	0	0	0	7	4	11
52.....	1	5	6	0	1	1	1	6	7
53.....	7	3	10	3	0	3	10	3	13
54.....	4	8	12	0	0	0	4	8	12
55.....	4	8	12	1	0	1	5	8	13
56.....	6	4	10	1	0	1	7	4	11
57.....	1	4	5	1	2	3	2	6	8
58.....	4	5	9	0	0	0	4	5	9
59.....	3	4	7	1	0	1	4	4	8

* Including one white child, aged 2, sex unknown.

TABLE 5.—DISTRIBUTION OF PELLAGRINS ACCORDING TO RACE, SEX AND AGE AT ONSET OF FIRST ERYTHEMA—(Continued)

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60.....	5	1	6	0	4	4	5	5	10
61.....	2	2	4	0	0	0	2	2	4
62.....	2	5	7	0	0	0	2	5	7
63.....	4	2	6	1	0	1	5	2	7
64.....	2	7	9	0	0	0	2	7	9
65.....	3	1	4	0	0	0	3	1	4
66.....	2	0	2	0	0	0	2	0	2
67.....	0	1	1	0	2	2	0	3	3
68.....	0	3	3	2	1	3	2	4	6
69.....	1	1	2	0	0	0	1	1	2
70.....	2	2	4	0	0	0	2	2	4
71.....	0	0	0	0	0	0	0	0	0
72.....	0	1	1	0	0	0	0	1	1
73.....	0	2	2	0	0	0	0	2	2
74.....	0	1	1	0	0	0	0	1	1
75.....	0	1	1	0	0	0	0	1	1
76.....	0	0	0	0	0	0	0	0	0
77.....	1	0	1	0	0	0	1	0	1
78.....	0	1	1	0	0	0	0	1	1
79.....	0	0	0	0	0	0	0	0	0
80.....	0	0	0	0	1	1	0	1	1
81.....	0	0	0	0	0	0	0	0	0
82.....	0	1	1	0	0	0	0	1	1
83.....	0	0	0	0	0	0	0	0	0
84.....	0	0	0	0	0	0	0	0	0
85.....	0	0	0	1	0	1	1	0	1
86.....	0	0	0	0	0	0	0	0	0
87.....	0	0	0	0	0	0	0	0	0
88.....	0	0	0	0	0	0	0	0	0
89.....	0	0	0	0	0	0	0	0	0
Total, age known	699	310	1,010*	115	36	151	814	346	1,161*
Age unknown.....	13	4	17	2	0	2	15	4	19
Total	712	314	1,027*	117	36	153	829	350	1,180*

* Including one white child, aged 2, sex unknown.

according to age at the time of onset, of the total 1,180 pellagrins is shown graphically in Figure 2; of the 712 white females in Figure 3; of the 314 white males in Figure 4, and of the 117 colored females and thirty-six colored males in Figure 5.

One important point brought out here is the occurrence of fourteen initial attacks of pellagra before the age of two years, three of them in the first year of life and eleven in the second. These fourteen cases amount to more than 1 per cent. of the total 1,180 cases, a proportion somewhat greater than that shown in the previous study⁵ of 253 pellagrins according to age at onset of the disease, in which series there were only two individuals under the age of two years.

5. Siler, Garrison and MacNeal: *THE ARCHIVES INT. MED.*, 1915, xv, 106; Second Progress Report, 1915, 121.

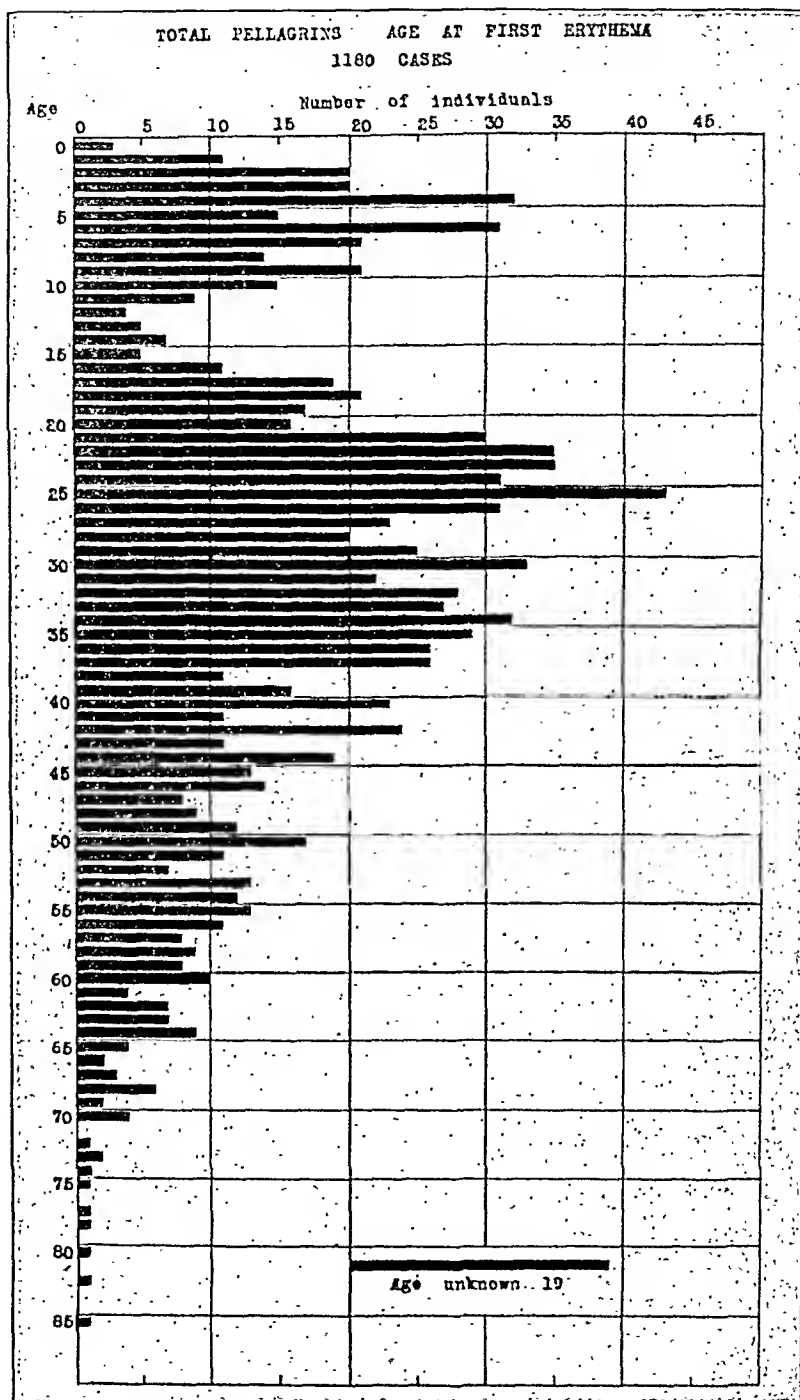


Fig. 2.—The distribution, according to age in years at the onset of the initial erythema, is shown for 1,161 pellagrins. In nineteen cases the age at onset could not be ascertained. One white child, aged 2, whose sex was not recorded, is also included here.

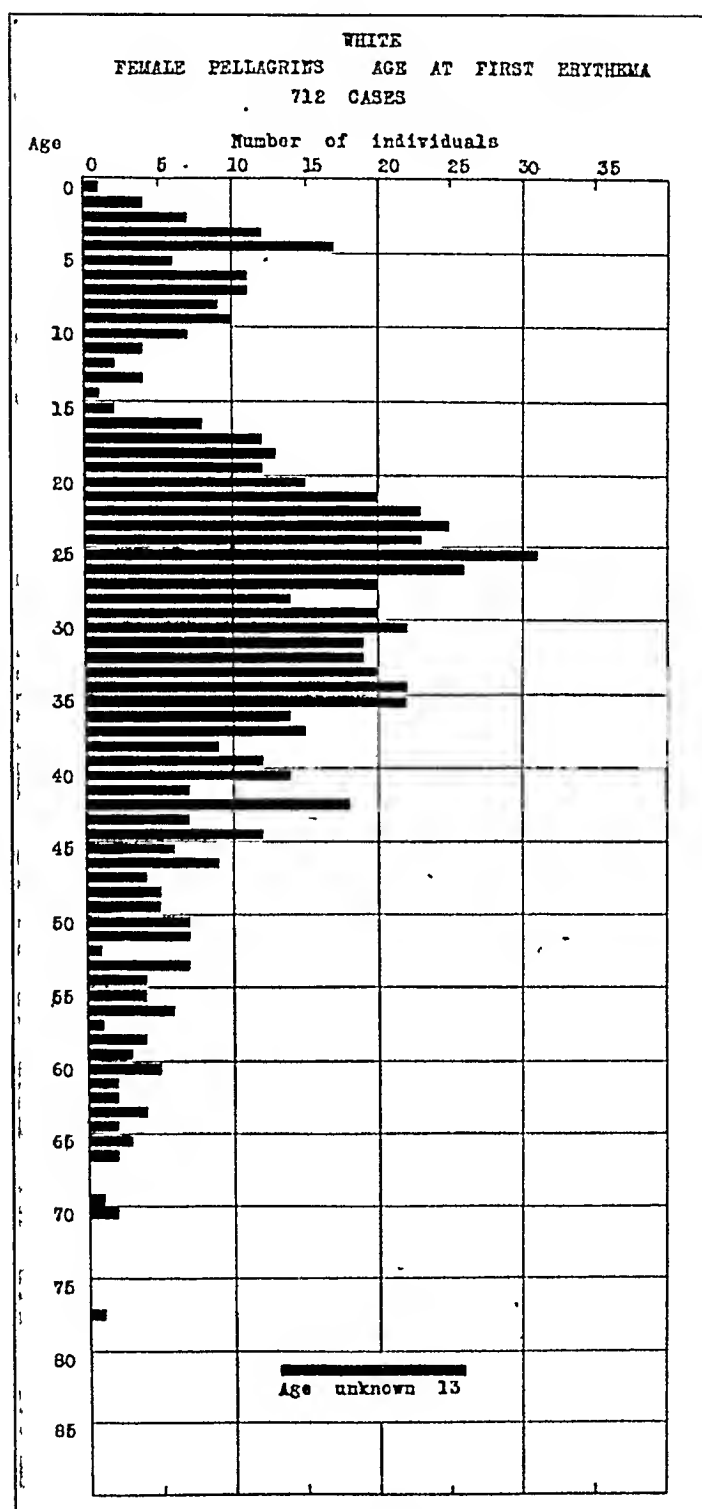


Fig. 3.—The distribution, according to age in years at the onset of the initial erythema, is shown for 699 white female pellagrins. In thirteen cases the age at onset could not be ascertained.

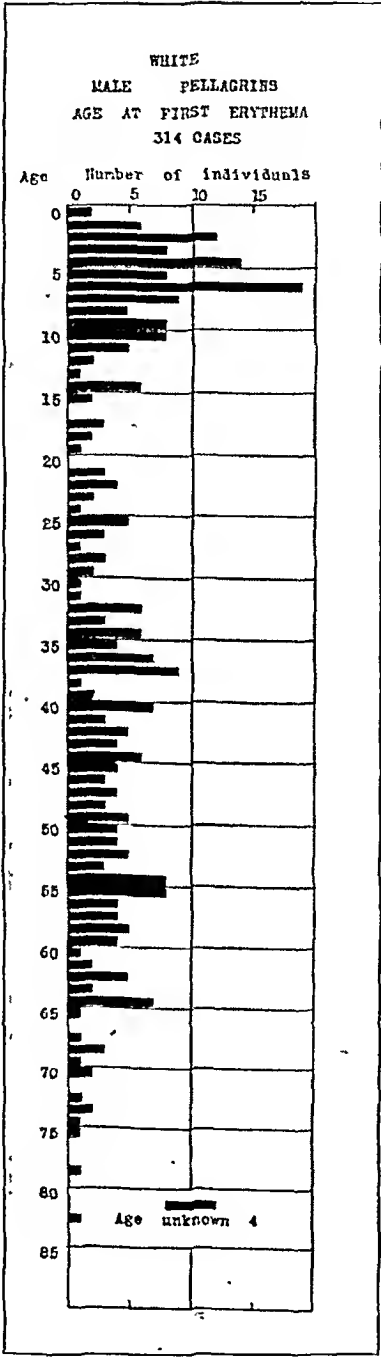


Fig. 4.—The distribution, according to age in years at the onset of the initial erythema, is shown for 310 white male pellagrins. In four cases the age at onset could not be ascertained.

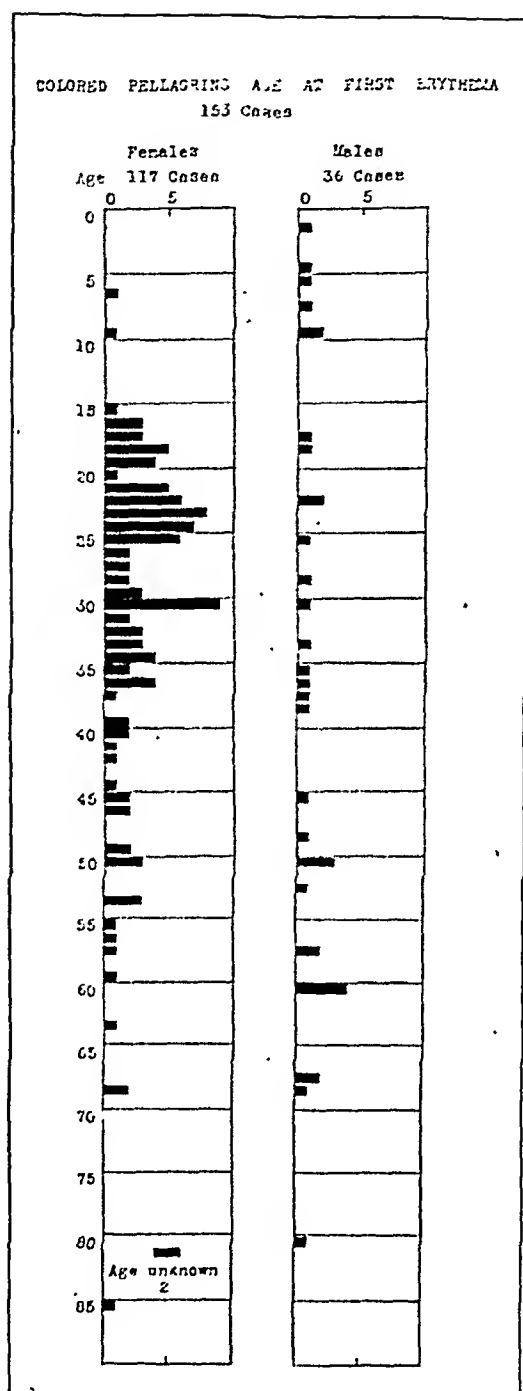


Fig. 5.—The distribution, according to age in years at the onset of the initial erythema, is shown for 115 colored female pellagrins and thirty-six colored male pellagrins. In two of the colored female pellagrins the age at onset could not be ascertained.

These fourteen cases, which originated before the age of two years, are perhaps worthy of a detailed consideration.

Pellagrin 120: I. L., girl, was born in October, 1909. The initial attack of pellagra began June 1, 1911, at the age of 19 months, with recovery. She had measles in January, 1912, and died of dysentery after a week's illness in April, 1912. Whether this dysentery was or was not a manifestation of pellagra is uncertain. There was no pellagra in any other member of the family. An adult pellagrin, No. 353, residing next door, suffered a severe recurrent attack of pellagra, lasting all summer, in 1911, and died of it in November, 1911. An unrelated woman, Pellagrin 678, living in the same house with the child, Pellagrin 120, suffered an initial attack of pellagra at about the same time as the child. This case, Pellagrin 120, was reported to us by Dr. A. W. Nelson of Spartanburg and was not seen by any member of our commission.

Pellagrin 173: A. J., boy, was born in March, 1910. The onset of the initial erythema occurred in June, 1911, at the age of 15 months. The case was seen and diagnosed by Dr. J. W. Babcock of Columbia, S. C. There were no recurrences in 1912, 1913 or 1914. This boy's mother, Pellagrin 171, had her initial attack of pellagra in October, 1910, six months after the child's birth, and she had a recurrent attack in April, 1911, two months before the onset of the erythema in the child. These attacks of pellagra were not seen by any member of our commission.

Pellagrin 179: R. L. R., boy, was born June 10, 1910. The initial erythema began in February, 1912, at the age of 20 months, on the backs of the hands and wrists, and it was accompanied by diarrhea. The erythema appeared on the feet in June and this was still desquamating when the patient was seen by us Aug. 23, 1912. The erythema recurred on hands and feet in 1913 and again in 1914 and the little boy died in July, 1914. The older sister of this child, Pellagrin 310, is said by the parents to have had the same disease when she died in August, 1910, at the age of 4 years. A paternal aunt, Pellagrin 170, living in the same house, developed pellagra for the first time in June, 1911, and had a severe recurrence in 1912. In February, 1911, this child, Pellagrin 179, with his parents, moved to another house, next door but one to the former residence, and it was at this new residence that the symptoms of pellagra appeared, in February, 1912.

Pellagrin 184: W. B., colored boy, was born March 4, 1911. The initial attack of pellagra began with erythema and dysentery on June 7, 1912, at the age of 15 months, and terminated in death July 6, 1912. The child had been weaned on May 25, only a short time before the onset of pellagra, but he had been eating an indiscriminate diet since the age of 5 months. The child's mother, Pellagrin 183, developed her initial attack of pellagra June 1, 1912, a few days before the onset of the erythema in his case. A paternal aunt of the child, Pellagrin 67, visited this family during May and June of 1912, and the onset of her cutaneous eruption occurred at their home on May 22, 1912. The disease appeared in her sister-in-law, Pellagrin 183, and nephew, Pellagrin 184, in less than three weeks after the appearance of the erythema in their guest. This child was seen by Dr. J. C. Moore of Duncan, S. C., who made the diagnosis, and the family was interviewed by us in August, 1912, six weeks after the child's death.

Pellagrin 643: L. O. A., girl, was born Aug. 23, 1907. The initial attack of pellagra began in July, 1909, at the age of 22 months, and the disease recurred in the summer of 1910. There was no recurrence in 1911, 1912, 1913 or 1914. The case originated in an endemic focus of pellagra outside of Spartanburg County and moved into this county at a later date. There were no other known pellagrins in the family. The diagnosis of this infantile case rests entirely upon the history.

Pellagrin 645: F. S., boy, was born Sept. 24, 1909. The onset of pellagra occurred, according to the mother, in March, 1910, at the age of 6 months.

The disease recurred in the summer of 1911 and again in 1912, but there was no recurrence in 1913 or 1914. His mother, Pellagrin 644, had her initial attack of pellagra in April, 1909, five months before his birth, and she had mild recurrences in 1910, 1911, 1912 and 1913, but no recurrence in 1914. Her mother, the maternal grandmother of Pellagrin 645, is also a pellagrin, Case 83, with onset in 1910. This family was first seen by us in 1913 and the diagnosis of infantile pellagra rests entirely upon the history.

Pellagrin 672: B. D., boy, was born in the spring or summer of 1910. The onset of pellagra occurred in the summer of 1911, at the approximate age of 1 year. There was no recurrence in 1912, 1913 or 1914. The boy's paternal grandfather, Pellagrin 131, lived in the same household. He had suffered his first attack of pellagra in 1910 and had a severe recurrence early in the spring of 1911, preceding the onset of the disease in the child. The child's father, mother and sister have not shown any signs of the disease. This case occurred before the beginning of our field work and the diagnosis of infantile pellagra rests entirely upon the history.

Pellagrin 888: F. E., boy, was born Aug. 18, 1908. The onset of pellagra occurred, according to the parents, in March, 1909, at the approximate age of 6 months. The disease recurred each spring, 1910, 1911, 1912, 1913 and 1914. There are no other known pellagrins in the family and only a history of visiting at the house of a pellagrin during early infancy. This case came under our observation for the first time in 1914. The patient was seen, however, by Dr. J. J. Allen of Enoree, S. C., in the spring of 1909, and he states that pellagra actually was present at the age of 6 months, evidenced by characteristic erythema of the hands and feet and well-marked gastro-intestinal symptoms.

Pellagrin 1010: D. T., boy, was born Oct. 3, 1912. The initial attack of pellagra began in June, 1914, at the age of 20 months. There were no other known pellagrins in the family. This boy contracted the disease while living in an endemic focus in a neighboring county and came under our observation when the family moved to Spartanburg in June, 1914. The attack of pellagra was very definite and the eruption quite typical. It was still present at our last recorded observation, Aug. 12, 1914.

Pellagrin 941: C. L. C., girl, was born June 23, 1912. Her initial pellagrous erythema began May 1, 1914, at the age of 22 months. She was seen by us on June 14, 1914, when a typical erythema of the backs of the hands was still present. A maternal uncle, Pellagrin 449, came to make his home with this family in August, 1912. He had had an attack of pellagra in 1912 and possibly also in 1911. There was a severe recurrence in March, 1913, and again in May, 1914, resulting in death at the Pellagra Hospital on May 30, 1914. Another maternal uncle of this baby, Pellagrin 856, who had been suffering from gastro-intestinal trouble for three years and had been adjudged insane in 1912, came on a visit to this family in May, 1913. A pellagrous erythema appeared upon his hands early in June, 1913. He left again in July and died of pellagra in North Carolina, Aug. 14, 1913. He probably had had the diagnostic erythema in previous years, but the evidence on this point is not conclusive. The baby's mother, Pellagrin 450, showed her first definite erythema in March or April, 1913, with recovery, and there was no recurrence in 1914. The baby slept with her uncle, Pellagrin 449, up to the time he was taken to the hospital.

Pellagrin 1026: T. L., girl, was born in November, 1912. The initial erythema appeared July 23, 1914, at the age of 20 months. The child's father, Pellagrin 529, developed his initial attack of pellagra on March 17, 1913, at a village about ten miles from Spartanburg. The attack was severe and, as he was unable to support his wife and child, all three were taken into the home of the wife's parents, who, although not in comfortable circumstances, were nevertheless somewhat above the average of mill workers in financial status. Six weeks later, on May 17, 1913, the wife's father, Pellagrin 530, came down with a severe initial attack of pellagra, from which he died on July 16.

1913, at the Pellagra Hospital, four days after admission. At about the same time, his wife, Pellagrini 1228, developed a mild erythema from which she soon recovered. A son of the old man lived just across the street and his wife, who was assisting in her father-in-law's household during this time of sickness, also developed her initial attack of pellagra about May 15, 1913, which proved to be mild in character. The original patient, Pellagrini 529 (patient's father), was sent away to the mountains of Tennessee on June 15, 1913, and he died there shortly afterward. The old lady, Pellagrini 1228, died early in 1914, without recurrence. The baby, Pellagrini 1026, showed her initial erythema in July, 1914, and was evidently recovering when seen by us on Aug. 6, 1914. No other members of the family had shown any evidence of pellagra up to that time.

Pellagrini 1133: W. B., boy, was born in 1911. The initial attack occurred in the spring of 1912 at the approximate age of 1 year, according to the history. The disease recurred in 1913 and there was a severe recurrence again in the early spring of 1914, with good recovery. This patient was seen by us for the first time in September, 1914, at which time there were, of course, no recognizable signs of pellagra.

Pellagrini 1164: O. M. D., boy, was born Dec. 27, 1912. The pellagrous erythema appeared on the hands, forearms, feet and legs in June, 1914, at the age of 18 months, but it was preceded by a persistent gastro-intestinal disorder, manifested by vomiting and diarrhea, which began March 30. Evidence of very typical desquamation was still present when seen by us Sept. 30, 1914. There were no other recognized cases of pellagra in the household. The family lived on a farm and the nearest known pellagrini was an aunt of the baby, Pellagrini 29, living two miles away, who suffered her first attack in 1910, with recurrences each year. A history of association with this aunt was not obtainable.

Pellagrini 1220: A. R. P., girl, was born Sept. 5, 1913. The onset of pellagra occurred in August, 1914, at the age of 11 months, with erythema on backs of hands, which later extended up the arms to the shoulders. When seen on October 3, there was still some desquamation on the arms and shoulders and the condition was considered to be pellagra, although an absolutely positive diagnosis could not be made from the appearance at that time. The child was still nursing its mother, but had also been taking solid food, chiefly wheat bread and sweet potato, for several months. The child's father, Pellagrini 1134, had his first attack of pellagra in June, 1913, about three months before the birth of the child and he suffered a recurrent attack in the summer of 1914. The mother of this child and a brother, aged 4, have shown no signs of pellagra.

The data in regard to these fourteen cases are briefly summarized in Table 6.

Certain characteristics of pellagra in early life are illustrated by these cases. In the first place, there are here only two examples of pellagra as early as the seventh month. Neither of these two patients was seen by us until some years after the onset of pellagra and in one case, Pellagrini 645, we have no authority for the diagnosis at this early age except the statements of members of the family. The subsequent history makes it very certain that the patient actually suffered from pellagra, but does not make certain the time of onset. The other case, Pellagrini 888, seems to be better established as an actual instance of onset at age of 6 months. During our field investigations we made a special search for infantile cases of pellagra and neglected no opportunity to see them. Most of the infantile cases reported to us proved

disappointing upon closer examination. We feel very certain therefore that definitely recognizable cases of pellagra in children under the age of 12 months have been extremely rare in Spartanburg County.

Another feature of interest is the evidence of very intimate association or the presence of an antecedent case of pellagra in the household where the infant has contracted the disease. In three instances, Pellagrins 173, 645 and 941, the mother had been a pellagrin for several months before the child developed the disease; in one instance the mother came down with pellagra at about the same time as the child, Pellagrin 184. In this latter case the disease was evidently introduced into the household by a paternal aunt visiting there. In another

TABLE 6.—THE FOURTEEN PELLAGRINS IN WHOM THE DISEASE APPEARED BEFORE THE AGE OF 2 YEARS

Pellagrin No.	Born	Onset of Pellagra	Age at Onset, Mos.	Recurrences	Authority for Diagnosis
645	Sept. 1909	Mar. 1910	6	1912, 1913	History only
888	Aug. 1908	Mar. 1909	6	1910, 1911, 1912, 1913, 1914	Dr. J. J. Allen
1,220	Sept. 1913	Aug. 1914	11	Seen, Oct. 3, 1914
672	1910	1911	12(?)	None	History only
1,133	1911	Spring 1912	12(?)	1913, 1914	History only
173	Mar. 1910	June 1911	15	None	Dr. J. W. Babcock
184	Mar. 1911	June 1912	15	Death, 1912	Dr. J. C. Moore
1,164	Dec. 1912	June 1914	18	Seen
120	Oct. 1909	June 1911	19	Death, 1912	Dr. A. W. Nelson
179	June 1910	Feb. 1912	20	1913, 1914, D.	Seen
1,010	Oct. 1912	July 1914	20	Seen
1,026	Nov. 1912	July 1914	20	Seen
941	June 1912	May 1914	22	Seen
643	Aug. 1907	July 1909	22	1910	History only

instance, Pellagrin 672, the paternal grandfather was the earlier case in the household; in two instances, Pellagrins 1,026 and 1,220, the child's father seems to have brought pellagra into the family. In one instance, Pellagrin 179, the earliest known case in the family was a sister, aged 4 years. Following this, the disease appeared in an aunt living in the same house, and after separation from this aunt the disease appeared in the young child, Pellagrin 179. In one instance, Pellagrin 120, the child developed pellagra simultaneously with an unrelated woman living in the same house, the nearest antecedent case being next door. In five instances, Pellagrins 643, 888, 1,010, 1,133 and 1,164 there were no other known pellagrins in the household. Three of these

cases (643, 888 and 1,133) arose previous to the beginning of our field work and their environments at the time could not be investigated. A fourth case, Pellagrin 1,010, originated in a neighboring county and the family moved into Spartanburg County on July 20, 1914, left the baby in the hospital and disappeared without giving us opportunity to obtain the desired information and about three weeks later the child was removed from the hospital by an aunt, who left no address. The fifth case, Pellagrin 1,164, originated in an isolated farm house, the nearest known pellagrin being an aunt two miles away, with whom there was no evident association. This series of cases in young children, therefore, furnishes more definite evidence of the dependence of incident pellagra upon close association with a preexisting case of the disease than is ordinarily found in the study of the disease as it originates in adults. This more clear-cut picture might be expected because of the relatively limited social intercourse of children under two years of age. It seems probable also that the incubation period of the disease is shorter and less variable in these young children than in older persons, which may also tend to simplify the problem.

It is interesting to note that in only four instances was the mother known to have pellagra and in only one instance, Pellagrin 645, did she have the disease previous to the birth of the child. When we bear in mind the relatively enormous prevalence of pellagra among child-bearing women in the endemic areas, it would seem remarkable that the simultaneous occurrence of pellagra in mother and infant child should be rare. A pellagrous father, grandfather, aunt or unrelated visitor in the household, considering the relative frequency of such association, seems to be as significant as the presence of a pellagrous mother. Child-bearing women make up a very large proportion of the cases of pellagra in Spartanburg County and an acute attack of pellagra is very frequently seen during the puerperium. The fact that young infants so rarely have pellagra and that only three children under the age of two years contracted the disease subsequent to its appearance in their mothers seems highly significant and indicates that the milk of pellagrous women cannot be regarded as an important agency in causing pellagra, either in the rôle of a vehicle of the hypothetical specific infectious or toxic causative agent or as a food deficient in elements, to the lack of which pellagra may be ascribed. Indeed one occasionally sees a happy, fat and healthy infant, whose only food has come from the breast of a pellagrous mother lying on her death-bed, and even if not well nourished and happy, it is nevertheless the rule for the children of pellagrous women to remain free from any sign of pellagra during infancy and especially during the period of exclusive breast-feeding. To those who are familiar with infantile beriberi and

its enormous prevalence and death rate in the Philippine Islands,⁶ the contrast between infantile pellagra and infantile beriberi will be sufficiently striking.

Of the fourteen cases, only one died in the initial attack of pellagra and this one was the only negro child in the group. All white children survived the year of onset. One of them, Pellagrin 184, died the following April of acute dysentery, without recurrence of skin lesions. Another, Pellagrin 179, survived the initial attack and a recurrence the following year and died in the third summer after the disease had recurred. The remaining eleven children were alive at our last observation of them.

In the age period between 2 and 12 years there were 198 instances of onset of pellagra. Their distribution according to race, sex and age at onset is shown graphically in Figures 2, 3, 4 and 5 and the data are printed, along with the data for the fourteen younger children, in Table 7. It will be noted that 212 of the total 1,180 recorded cases, or nearly 18 per cent., had their onset before the age of 12 years. This is important when we recall how little attention has been paid, relatively, to pellagra in children living in their own homes. Of the 212 children, 204 were white and eight were colored, a ratio of 25.5 to 1, indicating that pellagra in this county has been relatively much more rare in negro children than in adult negroes. This is in accord with the hypothesis previously suggested, that pellagra has not as yet established itself as an endemic disease among the negroes of this county

6. The age distribution of deaths from beriberi in Manila, according to the government reports compiled from data in Quarterly Report of Bureau of Health of the Philippine Islands is as shown in the following tabulation:

Age	1912			1913			1914		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Under 1.....	397	490	887	317	370	687	389	510	899
1 to 4.....	29	27	56	7	13	20	20	8	28
5 to 9.....	2	2	4	7	4	11	2	4	6
10 to 14.....	5	3	8	1	3	4	1	1	2
15 to 19.....	3	16	19	3	8	11	5	11	16
20 to 29.....	7	11	18	10	6	16	13	6	19
30 to 39.....	10	16	26	12	13	25	14	17	31
40 to 49.....	4	26	30	5	27	32	3	17	20
Over 50.....	14	28	42	10	12	22	6	15	21
Total.....	471	619	1,090	372	456	828	453	589	1,042

to the same degree as in the white race. The negro children, being the most completely segregated portion of their race, are relatively least afflicted with pellagra.

In the whole group of 212 children there were seven deaths in the year of the initial attack: three in white girls, age at onset being 4, 8 and 10 years; two in white boys, age at onset being 3 and 11 years; two in colored boys, age at onset being 1 and 5 years, respectively. The indicated death rate in first attack for children under 12 years is therefore quite low, 2.5 per cent. for white children, 25 per cent. for colored children and 3.3 per cent. for all the children considered together. The group of pellagrins originating in the age period from 2 to 12 years is of peculiar interest because of the large number of cases and the low mortality in the year of onset.

TABLE 7.—PELLAGRINS WITH ONSET AT AGE BELOW 12 YEARS, DISTRIBUTED ACCORDING TO RACE, SEX AND AGE AT ONSET OF THE INITIAL ERYTHEMA

	Age in Years												Total
	0	1	2	3	4	5	6	7	8	9	10	11	
White girls.....	1	4	7	12	17	6	11	11	9	10	7	4	99
White boys.....	2	6	12	8	14	8	19	9	5	8	8	5	104
Colored girls....	0	0	0	0	0	0	1	0	0	1	0	0	2
Colored boys....	0	1	0	0	1	1	0	1	0	2	0	0	6
Total.....	3	11	20*	20	32	15	31	21	14	21	15	0	212*

* Including one white child, aged 2, of unknown sex.

The age period from 12 to 16 years shows only twenty-one initial attacks of pellagra, nine in white girls, eleven in white boys and one in a colored girl aged 15. Of the twenty-one incident cases, only one died in the year of onset, Pellagrin 475, a white girl, aged 13. The low incidence of pellagra in these four years is in marked contrast to the incidence in younger persons of both sexes and to that in older women.

Up to the age of 16, the difference between boys and girls has been slight, although one may see indication of a greater tendency for boys to get pellagra under the age of 3. The greatest contrast on the other hand is shown between the white race and the colored race. Of the whole group of 233 incident cases under 16 years of age, 224 were white and only nine were colored persons, a ratio of 25 to 1. Taken in connection with the undoubtedly inferior food of the negroes in this county, as regards quality, quantity and variety, together with the

equally certain greater relative segregation of the negro children from association with pellagrins, these facts seem highly significant for the problem of the etiology of pellagra and may not be without value in considering the prevention of the disease. After the age of 16 the sex distinction in pellagra incidence becomes very prominent, but the racial relationships are not without interest. The distribution of the incident cases in the four years from age 16 to age 20 is shown in Table 8. The remarkable difference in sex incidence of pellagra in this population, namely the great excess of female pellagrins over male pellagrins, has been pointed out in our previous reports. Here it is strikingly shown that this difference becomes manifest at about the seventeenth year of life and the change from the relative equality of the earlier years is a sharp one.

TABLE 8.—PELLAGRINS WITH INITIAL ATTACK BETWEEN AGES 16 AND 20, DISTRIBUTED ACCORDING TO RACE, SEX AND AGE AT ONSET

	Age in Years				
	16	17	18	19	Total
White women.....	8	12	13	12	45
White men.....	0	3	2	1	6
Colored women.....	3	3	5	4	15
Colored men.....	0	1	1	0	2
Total women.....	10	16	18	16	60
Total men.....	0	4	3	1	8
Grand total.....	10	20	21	17	68

Another remarkable feature of the table is the relatively high incidence in colored women, fifteen colored women and forty-five white women, a ratio of 1 to 3. Previous to the age 16, in the data considered above, there were three colored girls, one of them 15 years old, and 108 white girls, the ratio being 1 to 36. The enormous rise in pellagra incidence in negro women in the age period from 16 to 20 years is not only very great as compared with younger negroes, but it is relatively enormous in comparison even with the large increase in incidence in white women which takes place at this time. Among the possible explanations for this greater increase in pellagra incidence in adolescent colored women, may be mentioned the somewhat earlier and somewhat more sudden change to the adult state in the negro race. This may play some part. Another possible factor, which seems to us of great importance, is the closer association with the white race which

the negro women experience at about this time. Many of them are engaged in domestic service or as day nurses to care for children. In many instances childbearing begins before the age of twenty, and this may also play a part. It has been impossible to get reliable histories in most of these cases of colored women, and it seems not worth while to go into details in regard to them. In only a few cases was there evidence of close association with antecedent cases of pellagra and in only three instances were there earlier cases of pellagra in the household. In three other instances a history of domestic service, such as cooking and washing clothes for mill-village people, was obtained. One patient gave birth to an illegitimate child in the year following the onset of pellagra.

The deaths during the year of initial attack for the age period 16 to 20 years are shown in Table 9. The characteristic racial difference in death rate is again evident here.

TABLE 9.—DEATH RATE FROM PELLAGRA DURING THE YEAR OF INITIAL ATTACK IN THE AGE PERIOD 16 TO 20 YEARS

	White			Colored			Both Races		
	Women	Men	Total	Women	Men	Total	Women	Men	Total
Initial attacks... ..	45	6	51	15	2	17	60	8	68
Deaths in initial attack..	3	0	3	7	1	8	10	1	11
Mortality per cent.	6.7	0.0	5.9	46.7	50.0	47.1	16.7	12.5	16.2

From the age of 20 years to that of 50 years the women show a very much higher incidence of pellagra than the men, the disparity being greater in the earlier years and gradually approaching equality at age 50. The number of initial attacks in each five-year period after age 20 is shown in Table 10. The number of female pellagrins is enormously greater than the number of male pellagrins in the third decade of life, but in the later age periods the number of women attacked diminishes rapidly while the number of men increases somewhat, and after age 55 years the female pellagrins are actually less numerous than the male.

The death rate in year of initial attack for each race and sex, by decades after age 20, is shown in Table 11. For the women the figures are large enough to indicate a consistent increase in the death rate in initial attack correlated with increased age at onset, ranging from 4.6 per cent. in the third decade to 47.6 per cent. in the seventh decade. For the other three groups the number of cases is somewhat small and deductions correspondingly less reliable. The death rate

TABLE 10.—INITIAL ATTACKS OF PELLAGRA IN EACH RACE AND SEX BY FIVE-YEAR PERIODS AFTER AGE 20

Age	White			Colored			Both Races		
	Women	Men	Total	Women	Men	Total	Women	Men	Total
20 to 24.....	106	10	116	27	4	31	133	14	147
25 to 29.....	111	14	125	15	2	17	126	16	142
30 to 34.....	102	17	119	21	2	23	123	19	142
35 to 39.....	72	23	95	9	4	13	81	27	108
40 to 44.....	58	25	83	5	0	5	63	25	88
45 to 49.....	29	19	48	6	2	8	35	21	56
50 to 54.....	26	24	50	6	4	10	32	28	60
55 to 59.....	18	25	43	4	2	6	22	27	49
60 to 64.....	15	17	32	1	4	5	16	21	37
65 to 69.....	6	6	12	2	3	5	8	9	17
70 to 74.....	2	6	8	0	0	0	2	6	8
75 to 79.....	1	2	3	0	0	0	1	2	3
80 to 84.....	0	1	1	0	1	1	0	2	2
85 to 89.....	0	0	0	1	0	1	1	0	1

TABLE 11.—DEATHS IN YEAR OF ONSET OF PELLAGRA FOR EACH RACE AND SEX, ACCORDING TO AGE BY DECADES AFTER AGE 20

	Decades							
	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	Total
White Women								
Initial attacks..	217	174	87	44	21	3	0	546
Deaths.....	10	17	13	14	10	1	0	65
Rate, per cent. ..	4.6	9.8	14.9	31.8	47.6	32.3	11.9
White Men								
Initial attacks..	24	40	44	49	23	8	1	189
Deaths.....	4	8	7	12	5	3	1	40
Rate, per cent. ..	16.7	20.0	15.9	24.5	21.7	37.5	100.0	21.2
Colored Women								
Initial attacks..	42	30	11	10	3	0	1	97
Deaths.....	13	13	7	4	2	0	0	39
Rate, per cent. ..	31.0	43.3	63.6	40.0	66.7	0.0	49.2
Colored Men								
Initial attacks..	6	6	2	6	7	0	1	28
Deaths.....	2	3	0	3	5	0	1	14
Rate, per cent. ..	33.3	50.0	0.0	50.0	71.4	100.0	59.0

TABLE 12.—DISTRIBUTION, ACCORDING TO RACE, SEX AND AGE AT ONSET OF INITIAL ERYTHEMA, OF THE 187 PELLAGRINS WHO DIED IN THE YEAR OF THE INITIAL ATTACK

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0.....	0	0	0	0	0	0	0	0	0
1.....	0	0	0	0	1	1	0	1	1
2.....	0	0	0	0	0	0	0	0	0
3.....	0	1	1	0	0	0	0	1	1
4.....	1	0	1	0	0	0	1	0	1
5.....	0	0	0	0	1	1	0	1	1
6.....	0	0	0	0	0	0	0	0	0
7.....	0	0	0	0	0	0	0	0	0
8.....	1	0	1	0	0	0	1	0	1
9.....	0	0	0	0	0	0	0	0	0
10.....	1	0	1	0	0	0	1	0	1
11.....	0	0	0	0	0	0	0	0	0
12.....	0	1	1	0	0	0	0	1	1
13.....	1	0	1	0	0	0	1	0	1
14.....	0	0	0	0	0	0	0	0	0
15.....	0	0	0	0	0	0	0	0	0
16.....	1	0	1	2	0	2	3	0	3
17.....	0	0	0	1	0	1	1	0	1
18.....	1	0	1	3	1	4	4	1	5
19.....	1	0	1	1	0	1	2	0	2
20.....	0	0	0	0	0	0	0	0	0
21.....	3	1	4	0	0	0	3	1	4
22.....	0	1	1	1	1	2	1	2	3
23.....	0	0	0	4	0	4	4	0	4
24.....	2	1	3	3	0	3	5	1	6
25.....	2	1	3	4	0	4	6	1	7
26.....	0	0	0	1	0	1	1	0	1
27.....	1	0	1	0	0	0	1	0	1
28.....	0	0	0	0	1	1	0	1	1
29.....	2	0	2	0	0	0	2	0	2
30.....	1	0	1	4	1	5	5	1	6
31.....	1	0	1	0	0	0	1	0	1
32.....	1	1	2	1	0	1	2	1	3
33.....	3	0	3	1	0	1	4	0	4
34.....	3	2	5	1	0	1	4	2	6
35.....	2	2	4	1	1	2	3	3	6
36.....	2	1	3	4	0	4	6	1	7
37.....	2	1	3	0	0	0	2	1	3
38.....	1	0	1	0	1	1	1	1	2
39.....	1	1	2	1	0	1	2	1	3
40.....	5	3	8	2	0	2	7	3	10
41.....	1	0	1	0	0	0	1	0	1
42.....	2	1	3	0	0	0	2	1	3
43.....	1	0	1	0	0	0	1	0	1
44.....	0	0	0	1	0	1	1	0	1
45.....	0	2	2	1	0	1	1	2	3
46.....	3	1	4	2	0	2	5	1	6
47.....	1	0	1	0	0	0	1	0	1
48.....	0	0	0	0	0	0	0	0	0
49.....	0	0	0	1	0	1	1	0	1
50.....	2	3	5	2	2	4	4	5	9
51.....	0	0	0	0	0	0	0	0	0
52.....	2	3	5	0	1	1	2	4	6
53.....	1	1	2	1	0	1	2	1	3
54.....	1	2	3	0	0	0	1	2	3
55.....	2	1	3	1	0	1	3	1	4
56.....	2	1	3	0	0	0	2	1	3
57.....	0	1	1	0	0	0	0	1	1
58.....	3	0	3	0	0	0	3	0	3
59.....	1	0	1	0	0	0	1	0	1

TABLE 12.—DISTRIBUTION, ACCORDING TO RACE, SEX AND AGE AT ONSET OF INITIAL ERYTHEMA, OF THE 187 PELLAGRINS WHO DIED IN THE YEAR OF THE INITIAL ATTACK—(Continued)

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60.....	3	0	3	0	3	3	3	3	6
61.....	2	0	2	0	0	0	2	0	2
62.....	0	1	1	0	0	0	0	1	1
63.....	2	1	3	0	0	0	2	1	3
64.....	0	2	2	0	0	0	0	2	2
65.....	2	0	2	0	0	0	2	0	2
66.....	1	0	1	0	0	0	1	0	1
67.....	0	1	1	0	1	1	0	2	2
68.....	0	0	0	2	1	3	2	1	3
69.....	0	0	0	0	0	0	0	0	0
70.....	1	2	3	0	0	0	1	2	3
71.....	0	0	0	0	0	0	0	0	0
72.....	0	0	0	0	0	0	0	0	0
73.....	0	0	0	0	0	0	0	0	0
74.....	0	0	0	0	0	0	0	0	0
75.....	0	1	1	0	0	0	0	1	1
76.....	0	0	0	0	0	0	0	0	0
77.....	0	0	0	0	0	0	0	0	0
78.....	0	0	0	0	0	0	0	0	0
79.....	0	0	0	0	0	0	0	0	0
80.....	0	0	0	0	1	1	0	1	1
81.....	0	0	0	0	0	0	0	0	0
82.....	0	1	1	0	0	0	0	1	1
83.....	0	0	0	0	0	0	0	0	0
84.....	0	0	0	0	0	0	0	0	0
Total, age known.	72	42	114	46	17	63	118	59	177
Age unknown.....	6	3	9	1	0	1	7	3	10
Total.....	78	45	123	47	17	64	125	62	187

in first attack seems to be more uniform for the white men, but there is some increase toward old age and the death rate of the whole group is nearly twice as high as for the white women. In the negroes over 20 years of age the death rate in first attack is nearly 50 per cent., somewhat higher for men than women and somewhat higher in the later decades of life. The number of cases available here is small, especially in the group of colored men.

In Table 12 are presented the detailed data in regard to race, sex and age at onset of pellagra of all the 187 patients who died in the year of the initial attack.

AGE DISTRIBUTION OF PELLAGRINS INCIDENT IN EACH YEAR

The distribution according to race, sex and age at onset, by five-year periods, of the incident cases of pellagra in each year after 1907 and for all those with onset previous to 1908, is shown in detail in Table 13. The data of these tables, although summarized into five-year

TABLE 13.—THE DISTRIBUTION OF INITIAL ATTACKS OF PELLAGRA IN DIFFERENT YEARS, ACCORDING TO RACE, SEX AND AGE AT TIME OF ONSET, BY FIVE-YEAR AGE PERIODS

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Before 1908									
0 to 4	1	0	1	0	0	0	1	0	1
5 to 9	0	0	0	0	0	0	0	0	0
10 to 14	0	0	0	0	0	0	0	0	0
15 to 19	3	0	3	2	0	2	5	0	5
20 to 24	10	0	10	0	0	0	10	0	10
25 to 29	2	0	2	0	0	0	2*	0	2
30 to 34	5	1	6	1	1	2	6	2	8
35 to 39	5	1	6	1	0	1	6	1	7
40 to 44	4	3	7	0	0	0	4	3	7
45 to 49	4	1	5	0	0	0	4	1	5
50 to 54	3	1	4	1	0	1	4	1	5
55 to 59	2	3	5	0	0	0	2	3	5
60 to 64	0	2	2	0	0	0	0	2	2
65 to 69	0	0	0	0	0	0	0	0	0
Over 70	0	0	0	0	0	0	0	0	0
Age unknown	0	0	0	0	0	0	0	0	0
Total.....	39	12	51	5	1	6	44	13	57
1908									
0 to 4	0	0	0	0	0	0	0	0	0
5 to 9	1	1	2	0	0	0	1	1	2
10 to 14	0	0	0	0	0	0	0	0	0
15 to 19	1	0	1	0	0	0	1	0	1
20 to 24	6	0	6	0	0	0	6	0	6
25 to 29	5	0	5	0	0	0	5	0	5
30 to 34	3	0	3	0	0	0	3	0	3
35 to 39	0	0	0	0	0	0	0	0	0
40 to 44	0	1	1	0	0	0	0	1	1
45 to 49	1	0	1	0	0	0	1	0	1
50 to 54	0	0	0	0	0	0	0	0	0
55 to 59	0	0	0	0	0	0	0	0	0
60 to 64	0	0	0	0	0	0	0	0	0
65 to 69	0	0	0	0	0	0	0	0	0
Age unknown	1	0	1	0	0	0	1	0	1
Total.....	18	2	20	0	0	0	18	2	20

TABLE 13.—THE DISTRIBUTION OF INITIAL ATTACKS OF PELLAGRA IN DIFFERENT YEARS, ACCORDING TO RACE, SEX AND AGE AT TIME OF ONSET, BY FIVE-YEAR AGE PERIODS—(Continued)

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
1909									
0 to 4	1	1	2	0	0	0	1	1	2
5 to 9	0	0	0	0	0	0	0	0	0
10 to 14	0	0	0	0	0	0	0	0	0
15 to 19	1	0	1	2	0	2	3	0	3
20 to 24	9	0	9	0	0	0	9	0	9
25 to 29	7	0	7	0	0	0	7	0	7
30 to 34	5	0	5	0	0	0	5	0	5
35 to 39	5	1	6	0	0	0	5	1	6
40 to 44	1	2	3	0	0	0	1	2	3
45 to 49	1	2	3	0	0	0	1	2	3
50 to 54	3	4	7	1	0	1	4	4	8
55 to 59	3	2	5	0	0	0	3	2	5
60 to 64	1	1	2	0	0	0	1	1	2
65 to 69	0	2	2	0	1	1	0	3	3
Over 70	0	0	0	0	0	0	0	0	0
Age unknown	0	1	1	0	0	0	0	1	1
Total.....	37	16	53	3	1	4	40	17	57
1910									
0 to 4	2	2	4	0	0	0	2	2	4
5 to 9	3	3	6	1	1	2	4	4	8
10 to 14	0	1	1	0	0	0	0	1	1
15 to 19	11	1	12	2	0	2	13	1	14
20 to 24	9	1	10	5	2	7	14	3	17
25 to 29	19	1	20	2	0	2	21	1	22
30 to 34	14	2	16	1	0	1	15	2	17
35 to 39	5	3	8	1	0	1	6	3	9
40 to 44	8	1	9	0	0	0	8	1	9
45 to 49	4	1	5	1	0	1	5	1	6
50 to 54	6	4	10	0	0	0	6	4	10
55 to 59	3	3	6	1	0	1	4	3	7
60 to 64	3	4	7	0	0	0	3	4	7
65 to 69	2	0	2	1	0	1	3	0	3
Over 70	1	2	3	0	0	0	1	2	3
Age unknown	3	1	4	0	0	0	3	1	4
Total.....	93	30	123	15	5	18	103	33	141

TABLE 13.—THE DISTRIBUTION OF INITIAL ATTACKS OF PELLAGRA IN DIFFERENT YEARS, ACCORDING TO RACE, SEX AND AGE AT TIME OF ONSET, BY FIVE-YEAR AGE PERIODS—(Continued)

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
1911									
0 to 4	5	12	18*	0	0	0	5	12	18*
5 to 9	5	5	10	0	1	1	5	6	11
10 to 14	2	8	10	0	0	0	2	8	10
15 to 19	11	3	14	1	1	2	12	4	16
20 to 24	20	1	21	3	0	3	23	1	24
25 to 29	24	3	27	5	0	5	29	3	32
30 to 34	21	2	23	4	1	5	25	3	28
35 to 39	16	6	22	1	0	1	17	6	23
40 to 44	17	6	23	0	0	0	17	6	23
45 to 49	6	5	11	0	1	1	6	6	12
50 to 54	3	4	7	2	0	2	5	4	9
55 to 59	3	8	11	2	0	2	5	8	13
60 to 64	2	2	4	0	1	1	2	3	5
65 to 69	2	0	2	0	0	0	2	0	2
Over 70	0	3	3	0	1	1	0	4	4
Age unknown	3	0	3	1	0	1	4	0	4
Total.....	140	68	209*	19	6	25	159	74	234*
1912									
0 to 4	9	7	16	0	1	1	9	8	17
5 to 9	11	14	25	1	0	1	12	14	26
10 to 14	7	3	10	0	0	0	7	3	10
15 to 19	10	1	11	3	0	3	13	1	14
20 to 24	11	3	14	8	1	9	19	4	23
25 to 29	14	4	18	1	0	1	15	4	19
30 to 34	15	6	21	6	0	6	21	6	27
35 to 39	17	2	19	0	0	0	17	2	19
40 to 44	9	8	17	1	0	1	10	8	18
45 to 49	2	5	7	1	0	1	3	5	8
50 to 54	2	1	3	0	2	2	2	3	5
55 to 59	2	7	9	1	0	1	3	7	10
60 to 64	4	3	7	1	0	1	5	3	8
65 to 69	0	1	1	0	1	1	0	2	2
Over 70	0	1	1	1	0	1	1	1	2
Age unknown	3	0	3	0	0	0	3	0	3
Total.....	116	66	182	24	5	29	140	71	211

* Including one white child aged 2, sex unknown.

TABLE 13.—THE DISTRIBUTION OF INITIAL ATTACKS OF PELLAGRA IN DIFFERENT YEARS, ACCORDING TO RACE, SEX AND AGE AT TIME OF ONSET, BY FIVE-YEAR AGE PERIODS—(Continued)

Age	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
1913									
0 to 4	13	10	23	0	0	0	13	10	23
5 to 9	9	11	20	0	1	1	9	12	21
10 to 14	4	6	10	0	0	0	4	6	10
15 to 19	6	2	8	2	1	3	8	3	11
20 to 24	24	4	28	4	1	5	28	5	33
25 to 29	27	4	31	4	2	6	31	6	37
30 to 34	27	1	28	6	0	6	33	1	34
35 to 39	15	5	20	4	2	6	19	7	26
40 to 44	9	2	11	2	0	2	11	2	13
45 to 49	5	4	9	1	1	2	6	5	11
50 to 54	6	5	11	1	1	2	7	6	13
55 to 59	3	0	3	0	1	1	3	1	4
60 to 64	4	2	6	0	3	3	4	5	9
65 to 69	0	2	2	0	0	0	0	2	2
Over 70	1	0	1	0	0	0	1	0	1
Age unknown	1	1	2	1	0	1	2	1	3
Total.....	154	59	213	25	13	38	179	72	251
1914									
0 to 4	10	10	20	0	1	1	10	11	21
5 to 9	18	15	33	0	1	1	18	16	34
10 to 14	5	4	9	0	0	0	5	4	9
15 to 19	4	1	5	4	0	4	8	1	9
20 to 24	17	1	18	7	0	7	24	1	25
25 to 29	13	2	15	3	0	3	16	2	18
30 to 34	12	5	17	3	0	3	15	5	20
35 to 39	9	5	14	2	2	4	11	7	18
40 to 44	10	2	12	2	0	2	12	2	14
45 to 49	6	1	7	3	0	3	9	1	10
50 to 54	3	5	8	1	1	2	4	6	10
55 to 59	2	2	4	0	1	1	2	3	5
60 to 64	1	3	4	0	0	0	1	3	4
65 to 69	2	1	3	1	1	2	3	2	5
Over 70	1	3	4	0	0	0	1	3	4
Age unknown	2	1	3	0	0	0	2	1	3
Total.....	115	61	176	26	7	33	141	68	209

periods, are still too detailed to give an immediate impression of the differences. The marked increase in pellagra up to 1911 and the somewhat slower increase since that time have been commented upon. Attention has also been called to the indication that relatively more negroes have been attacked in recent years. We wish, in this place, to direct especial attention to the age distribution.

TABLE 14.—SUMMARY OF AGE DISTRIBUTION OF INITIAL ATTACKS
IN DIFFERENT YEARS

	Age						Total
	0 to 9	10 to 14	15 to 19	20 to 49	Over 50	Unknown	
Before 1908.....	1	0	5	39	12	0	57
1908.....	2	0	1	16	0	1	20
1909.....	2	0	3	33	18	1	57
1910.....	12	1	14	80	30	4	141
1911.....	29	10	16	142	33	4	234
1912.....	43	10	14	114	27	3	211
1913.....	44	10	11	154	29	3	251
1914.....	55	9	9	105	28	3	209
Total.....	188	40	73	683	177	19	1,180

TABLE 15.—PROPORTION OF INITIAL ATTACKS IN CHILDREN
UNDER 12 YEARS OF AGE

	Before 1910	1910	1911	1912	1913	1914	Total
Total incident pellagrins.....	134	141	234	211	251	209	1,180
Incident pellagrins under 12 years....	5	13	33	48	51	62	212
Per cent.	3.7	9.2	14.1	22.7	20.3	29.7	18.0

The striking differences in age distribution of initial attacks of pellagra are shown in Table 14. In the early years, up to 1910, there were in the series only five cases in children out of a total of 134 cases, or 3.7 per cent. The ratio between initial attacks in children under 12 years and total initial attacks for each year after 1909 is shown in Table 15. It is evident that the proportion of children attacked by pellagra has increased very much since 1909 and that the proportion was greatest in 1914, when nearly 30 per cent. of the new cases were in children. This increase is in part only apparent because of the lack of attention to pellagra in children during the years previous to 1912,

but in a considerable degree, we believe, it represents a real increase in the proportion of children attacked by the disease. The actual number of children attacked shows a progressive increase each year to 1914, in which year sixty-two children are known to have contracted the disease.

It is well recognized that endemic areas of pellagra in noninstitutional populations are characterized by the presence of pellagrous children. This point has been emphasized by Sambon.⁷ Our observations of pellagra have also convinced us that the sporadic cases of pellagra and the first cases in a community are almost certain to occur in adults. The appearance of the disease in children, unless they are recent arrivals, at once suggests that the disease has gained a local foothold and that undoubted new cases are actually originating in the locality. In adults the actual place and time of origin is much less certain. We have in our series of cases several pellagrins in whom a recurrence appeared after two or more years of freedom from diagnostic symptoms and there is one instance of definite severe attack of pellagra in a woman, aged 61, in the year 1913, who gives a very clear history of similar attacks in the summers of 1893, 1894 and 1895, with complete absence of symptoms for eighteen years. Incidentally, it may be mentioned that this old woman recovered from the 1913 attack and has remained free from the eruption in 1914 and 1915. The occurrence of such cases as this calls into question to some extent the decision concerning place of origin of the disease in adults who have changed their place of abode. In children, on the other hand, the length of previous life is shorter and in most instances the individuals have remained within a relatively small area throughout life. We are inclined, also, to believe that the incubation period of pellagra is shorter and more uniform in children.

The rapid and progressive increase of pellagra in children in Spartanburg County may therefore be regarded as additional evidence of the rather recent extension of the disease in this area and as an indication that pellagra has been and is even now becoming more firmly established as an endemic disease of this locality. In other words, more homes and more families are now afflicted with this disease than in previous years.

INCIDENCE OF PELLAGRA PER 10,000 POPULATION

The population of Spartanburg County, according to the U. S. Census,⁸ was 65,560 in 1900 and 83,465 in 1910. If this increase continued at the same arithmetical rate after 1910, there has been added

7. Sambon, L. W.: Progress Report on the Investigation of Pellagra, *Jour. Trop. Med.*, 1910, xiii, 271, 287, 305, 319.

8. Thirteenth Census of the United States, 1910, iii, 664.

to this population 7,162 individuals from 1910 to 1914, and the estimated population in 1914 would be therefore 90,626. The same census shows that the colored population of the county was 21,167 in 1900 and 26,410 in 1910. The colored population in 1914, estimated in the same way, would be 28,507. We have been able to obtain directly from the Census Bureau, through courtesy of the U. S. Department of Commerce, more detailed statistics of the exact distribution, according to race, sex and age, of the population under 20 years of age, as well as for the age periods 20 to 44 years, and over 45 years. These data were printed in our first progress report.⁹ The U. S. Census¹⁰ for 1910 also shows the composition of the population of the whole state according to race, sex and age by five-year age periods to age 65, and beyond that by decades. Assuming that the age distribution in the whole state was not significantly different from the age distribution in Spartanburg County, we have divided the known county groups from age 20 to 44 and the known county groups of age 45 and over into five-year and ten-year age periods in the same proportion. Then by applying the formula for the arithmetic increase to each group of the total population, male and female, and to each group of the colored population, male and female, we have calculated their distribution by age periods in 1914. The distribution of the white population, that is, all not colored, has then been obtained by difference. The resulting data doubtless indicate the number of individuals of each race for each age period in the county in 1914 as accurately as is possible in the absence of an actual census taken in that year. Certainly they are sufficiently accurate for our present purpose of estimating the relative incidence of pellagra in various age periods in relation to age and sex. These data are shown in Table 16.

The ratio of total recorded incident attacks of pellagra up to the end of 1914, for each race and sex in each age period, to the respective population of the county in 1914 is shown in Table 17, expressed as incident cases per 10,000 of population. The figures represent total recorded cases in the county and not incidence per year, the total number of cases considered here (1,180) being more than four times the number recorded as originating in any one year (251 in 1913). The data of these tables are presented graphically in Figure 6. These pictures are different from those shown in Figures 2, 3, 4 and 5, because here the number of pellagrins at each age period has been divided by the total population of that age period, and of course the total population is largest in the earliest age period and tends to dimin-

9. Siler, J. F., and Garrison, P. E.: *An Intensive Study of the Epidemiology of Pellagra: Report of Progress*, *Am. Jour. Med. Sc.*, 1913, cxlvi, 44; *First Progress Report*, 1913, p. 19.

10. *Thirteenth Census of the United States*, 1910, iii, 654.

ish progressively to old age. Thus one finds that the twenty-five cases in white men in the age period 55 to 59 represent an incidence of 325 per 10,000 population at this age, whereas the forty-nine cases in the age period 5 to 9 represent an incidence of only 119 per 10,000 population at this age. The incidence rates for the white race for ages beyond

TABLE 16.—POPULATION OF SPARTANBURG COUNTY IN 1914 BY FIVE-YEAR AGE PERIODS TO AGE 65 AND SUBSEQUENTLY BY DECADES, CALCULATED FROM DATA OF U. S. CENSUS OF 1910 AND 1900

Age	White, Including All not Colored			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0 to 4	4,641	4,935	9,576	2,126	2,222	4,348	6,767	7,157	13,924
5 to 9	4,008	4,116	8,124	2,030	2,031	4,061	6,038	6,147	12,185
10 to 14	3,592	3,789	7,381	1,980	1,933	3,913	5,572	5,722	11,294
15 to 19	3,576	3,501	7,077	1,685	1,649	3,334	5,261	5,150	10,411
0 to 19	15,817	16,341	32,158	7,821	7,835	15,656	23,638	24,176	47,814
20 to 24	3,132	2,943	6,075	1,689	1,359	3,048	4,821	4,302	9,123
25 to 29	2,486	2,381	4,867	1,232	1,028	2,260	3,718	3,409	7,127
30 to 34	1,906	1,972	3,878	871	780	1,651	2,777	2,752	5,529
35 to 39	1,687	1,782	3,469	809	758	1,567	2,496	2,540	5,036
40 to 44	1,237	1,328	2,565	580	561	1,141	1,817	1,889	3,706
20 to 44	10,448	10,406	20,854	5,181	4,486	9,667	15,629	14,892	30,521
45 to 49	1,092	1,003	2,095	412	350	762	1,504	1,353	2,857
50 to 54	1,009	1,091	2,100	331	367	698	1,340	1,458	2,798
55 to 59	702	769	1,471	213	233	446	915	1,002	1,917
60 to 64	663	756	1,419	209	301	510	872	1,057	1,929
65 to 74	736	678	1,414	221	280	501	957	958	1,915
75 to 84	250	184	434	71	73	144	321	257	578
85 to 94	42	28	70	18	16	34	60	44	104
95 and over	7	4	11	6	4	10	13	8	21
45 and over	4,501	4,513	9,014	1,481	1,624	3,105	5,982	6,137	12,119
Age unknown	42	51	93	37	42	79	79	93	172
Total.....	30,808	31,311	62,119	14,520	13,987	28,507	45,328	45,298	90,626

TABLE 17.—RELATIVE INCIDENCE OF PELLAGRA IN RESPECT TO RACE, SEX AND AGE AT ONSET, BASED ON TOTAL RECORDED PELLAGRINS UP TO OCT. 15, 1914, AND POPULATION OF THE COUNTY IN 1914 ESTIMATED BY COMPUTATION FROM U. S. CENSUS OF 1900 AND 1910

White Race									
Age	Female			Male			Total		
	Popu- lation, 1914	Re- corded Pella- grins	Incidence per 10,000	Popu- lation, 1914	Re- corded Pella- grins	Incidence per 10,000	Popu- lation, 1914	Re- corded Pella- grins	Incidence per 10,000
0 to 4	4,641	41	88	4,935	42	85	9,576	84*	88
5 to 9	4,008	47	117	4,116	49	119	8,124	96	118
10 to 14	3,592	18	50	3,789	22	58	7,381	40	54
15 to 19	3,576	47	131	3,501	8	23	7,077	55	78
0 to 19	15,817	153	97	16,341	121	74	32,158	275*	86
20 to 24	3,132	106	338	2,943	10	34	6,075	116	191
25 to 29	2,486	111	447	2,381	14	59	4,867	125	257
30 to 34	1,906	102	535	1,972	17	86	3,878	119	307
35 to 40	1,687	72	427	1,782	23	129	3,469	95	274
40 to 44	1,237	58	469	1,328	25	188	2,565	83	324
20 to 44	10,448	449	430	10,406	89	86	20,854	538	258
45 to 49	1,092	29	266	1,003	19	189	2,095	48	229
50 to 54	1,009	26	258	1,091	24	220	2,100	50	238
55 to 59	702	18	256	769	25	325	1,471	43	292
60 to 64	663	15	226	756	17	225	1,419	32	226
65 to 74	736	6	82	678	12	177	1,414	18	127
75 to 84	250	2	80	184	3	163	434	5	115
85 to 94	42	1	238	28	0	0	70	1	148
Over 95	7	0	0	4	0	0	11	0	0
45 and over	4,501	97	216	4,513	100	222	9,014	197	219
Age unknown	42	13	51	4	93	17
Total.....	30,808	712	231	31,311	314	103	62,119	1,027*	165

* Including one child, aged 2, whose sex was not ascertained.

TABLE 17.—RELATIVE INCIDENCE OF PELLAGRA IN RESPECT TO RACE, SEX AND AGE AT ONSET, BASED ON TOTAL RECORDED PELLAGRINS UP TO OCT. 15, 1914, AND POPULATION OF THE COUNTY IN 1914 ESTIMATED BY COMPUTATION FROM U. S. CENSUS OF 1900 AND 1910—(Continued)

Colored Race									
Age	Female			Male			Total		
	Popu- lation, 1914	Re- corded Pella- grins	Inci- dence per 10,000	Popu- lation, 1914	Re- corded Pella- grins	Inci- dence per 10,000	Popu- lation, 1914	Re- corded Pella- grins	Inci- dence per 10,000
0 to 4	2,126	0	0	2,222	2	9	4,348	2	5
5 to 9	2,030	2	10	2,031	4	20	4,061	6	15
10 to 14	1,980	0	0	1,933	0	0	3,913	0	0
15 to 19	1,685	16	95	1,649	2	12	3,334	18	54
6 to 19	7,821	18	23	7,835	8	10	15,656	26	17
20 to 24	1,689	27	160	1,359	4	30	3,048	31	102
25 to 29	1,232	15	122	1,028	2	20	2,260	17	75
30 to 34	871	21	241	780	2	26	1,651	23	139
35 to 39	809	9	111	758	4	53	1,567	13	83
40 to 44	580	5	86	561	0	0	1,141	5	44
20 to 44	5,181	77	149	4,486	12	27	9,667	89	92
45 to 49	412	6	146	350	2	57	762	8	105
50 to 54	331	6	181	367	4	106	698	10	143
55 to 59	213	4	188	233	2	86	446	6	135
60 to 64	209	1	48	301	4	133	510	5	98
65 to 74	221	2	91	280	3	107	501	5	100
75 to 84	71	0	0	73	1	137	144	1	69
85 to 94	18	1	55	16	0	0	34	1	294
Over 95	6	0	0	4	0	0	10	0	0
45 and over	1,481	20	135	1,624	16	100	3,105	36	116
Age unknown	37	2	42	0	79	2
Total. ...	14,520	117	81	13,987	36	25	28,507	153	54

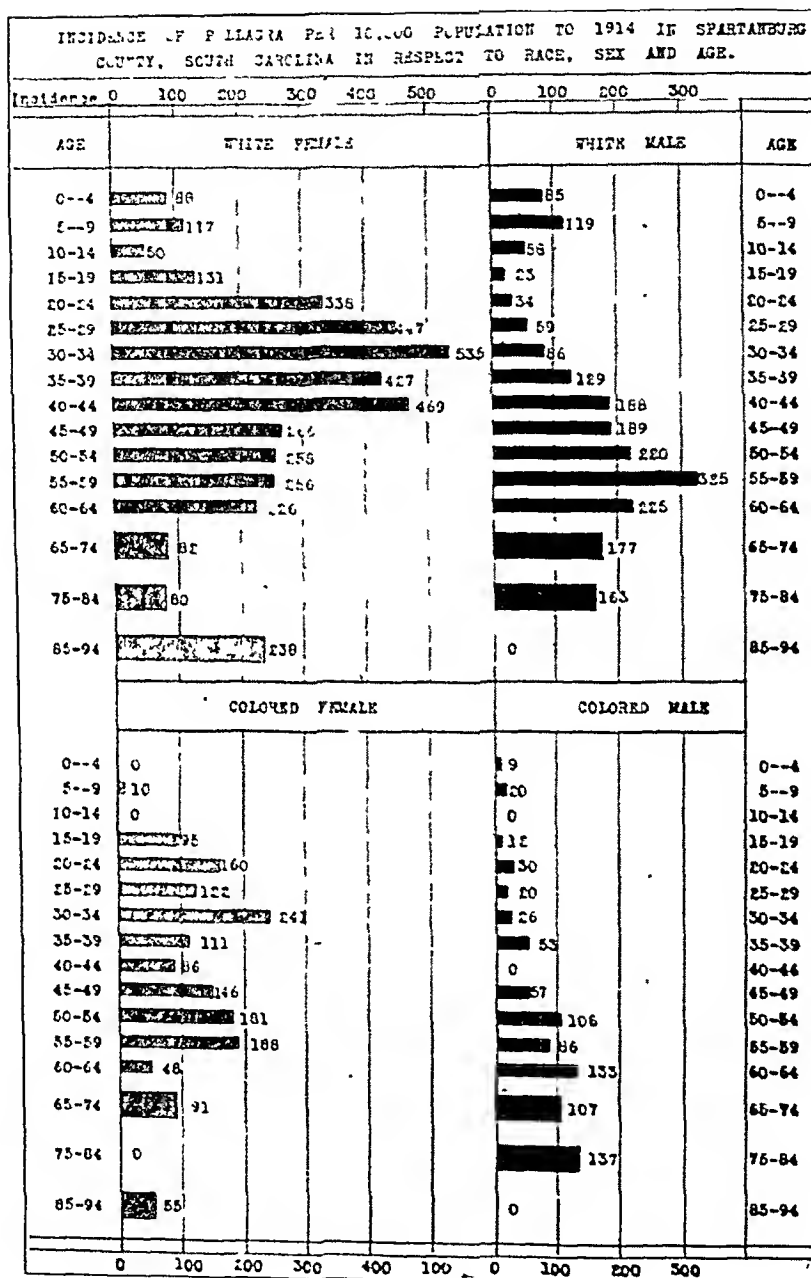


Fig. 6.—The incidence per 10,000 population has been computed from the calculated population of Spartanburg County in 1914 and the total recorded cases of pellagra in each five-year age period according to age at onset of the initial erythema. The broader columns after age of 65 apply to ten-year-age groups. The incidence per 10,000 for each age group is also indicated by the number placed at the end of the column.

age 75 and for the negro race beyond age 45 have little or no significance because of the very small groups of population.

In every instance there is a peak in the age period 5 to 9 followed by a fall in the period 10 to 14. In the next period, 15 to 19 years, the rise is sharp in the white female population, but especially sharp in the colored male and female. In fact it is in the ten years from 15 to 24 that the incidence of pellagra in negroes, both men and women, approaches most nearly the incidence rate of the disease in the white race of this county. In white women the rate ascends rapidly to reach the enormous incidence of 535 per 10,000 population in the age period 30 to 34, after which it gradually declines. The rate in white men ascends much more gradually, but in a progressive manner, reaching an incidence of 325 per 10,000 in the age period 55 to 59 years. In the negroes the incidence rate is everywhere lower than in the white race. For the negro women there is a rapid increase beginning at age 15 and reaching its height in the period 30 to 34 years, this being followed by a rapid decline and an irregular incidence beyond age 45, where the number of individuals is small. In negro men the number of individuals is so small that comparisons of different age periods are hardly warranted. The incidence rate on the whole is lower than that for any other of the three race-sex groups. Only after age 60 is there a distinct indication of a higher incidence in negro men than in negro women.

In this connection it may be mentioned that, next to negro children of both sexes, the adult negro men are most effectively segregated from social relationships with the white race in Spartanburg County, especially that portion of the white race which lives in the chief endemic foci of pellagra, namely, the cotton-mill villages. The adult negro man is to a very large extent a day laborer or a field worker in the open air, and his home is in general a cabin or a poorly constructed house, isolated on a farm or segregated in the negro quarter of a village or city. To this rule there are some exceptions, but they are relatively not numerous. The negro women also work in the field in many instances in addition to performing their household duties. Most of them are at some time employed by white families for domestic duties, some as house servants, but more in the capacity of washerwomen. The homes of the negro women are the same as the homes of the negro men and even when engaged as cooks and waitresses it is customary for the negro women to return to their homes at night. The data concerning food will, of course, be considered in a separate paper. It will suffice here to point out that the diet of the negroes is much inferior in quality, quantity and variety to that of the white race in this county.

In our opinion the relatively lower pellagra incidence in negroes in this county is due chiefly to their relative segregation from pel-

lagrins. They live in poorer houses, eat an inferior diet and are, as a whole, in much worse financial condition than the white race. On the other hand, they are socially segregated, their homes are for the most part either isolated cabins or are grouped in negro quarters of the city, town or village. Pellagra is not so persistently present among them as among the white race, furthermore, because the negro pellagrins die much more promptly than do the white pellagrins. The facts observed here in Spartanburg County in regard to racial and age differences in pellagra incidence indicate very strongly that poverty and poor diet are, as has long been known, factors of great moment in determining death rate from pellagra in those attacked, but that, as far as the original onset of the disease is concerned, they are of importance only in conjunction with close association with antecedent pellagrins or residence in an endemic area of the disease.

SUMMARY

1. The number of recognized incident cases of pellagra in Spartanburg County has increased progressively each year since 1907, very rapidly to 1911 and at a less rapid rate to 1914.

2. The death rate in year of initial attack was 15.8 per cent. for the total 1,180 recorded cases. There is no definite indication of a progressive change in the death rate in recent years, although it was apparently higher previous to 1911.

3. The disease has attacked the white race more than the negroes in this county, but in recent years there has been a slow but progressive increase in the ratio of incident negro pellagrins to incident white pellagrins.

4. The death rate in initial attack has been 41.8 per cent. for negroes and 12 per cent. for the white race.

5. Pellagra was very rarely observed under the age of 1 year. It was not so rare in the second year and fairly common in the age period from 2 to 12 years. The death rate in initial attack has been low in children.

6. Evidence of residence very close to an antecedent pellagrin has usually been quite clear in the cases of infantile pellagra.

7. The milk of pellagrous mothers cannot be regarded as the cause or the vehicle of the cause of pellagra in infants.

8. The age period 12 to 16 years is relatively free from initial attacks of pellagra.

9. After age 16 years pellagra incidence rises rapidly in women and the rise is especially sharp in colored women. In the latter group the death rate has been high, 46.7 per cent., in year of onset in the age period 16 to 20 years.

10. From age 20 to age 50 years, the number of women attacked by pellagra gradually diminishes and the number of men attacked gradually increases, so that the two sexes are approximately equal in this respect at age 50. In old age the onset of pellagra has been slightly more common in men in this population.

11. The death rate in first attack in white women over 20 years of age has been 11.9 per cent., increasing progressively from 4.6 per cent. in the third decade to 47.6 per cent. in the seventh decade of life. The death rate for analogous groups of white men, colored women and colored men has been 21.2 per cent., 40.2 per cent. and 50 per cent., respectively, with a slight tendency for the death rate to increase with age in all groups.

12. Pellagrins with onset under the age of 12 years were only 3.7 per cent. of the total recorded cases previous to 1910, but the proportion has increased to 29.7 per cent. of the total recorded onsets in the year 1914. These observations corroborate the other evidence of a distinct progressive increase of pellagra in this county in recent years.

13. The incidence per 10,000 population has been 231 for white female population, 103 for white male, 81 for colored female and 25 for colored male. In the age period 10 to 14 years the incidence is low in all groups. In white female population it is highest in the age period 30 to 34 years, namely 535 per 10,000; in white male, in the age period 55 to 59, namely 325 per 10,000; in colored female 241 per 10,000 in age period 30 to 34; in colored male 133 per 10,000 in age period 60 to 64.

14. The lower incidence rate and the higher death rate for those attacked have occurred in negroes in conjunction with greater poverty of this race and a diet poorer in quality, quantity and variety. Incidence has been lowest in the sex and age groups of negroes most completely segregated from white pellagrins.

THE LIME DEFICIENCY OF DIABETES*

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INTRODUCTION

Bocker¹ in 1853 and Neubauer² in 1856 reported that diabetic patients excreted more lime salts in their urine than normal individuals. In 1889 Toralbo³ came to a similar conclusion from his findings. Since that time many observations have been recorded, and the conclusion has been reached that diabetics suffer from a loss of calcium from their body. Some of these studies we shall review in detail.

Von Moraczewski⁴ in 1897 found in one case of diabetes mellitus, on a mixed diet, a retention of nitrogen and chlorin coincident with a loss of calcium and phosphorus, the phosphorus loss being nearly three times as great as the calcium loss. The phosphorus loss was 32 per cent. of the intake and the calcium loss 11 per cent. of the intake. On an animal diet containing much less chlorin and lime, and somewhat less phosphorus, the nitrogen balance remained positive, but the chlorin became negative, and the losses of phosphorus and calcium were increased. Von Moraczewski thought that the lime excretion was a specific symptom and that increasing the lime in the food decreased the sugar excretion.

A year later von Moraczewski⁵ (1898) published further balance data on diabetes mellitus. When added to a mixed diet, calcium phosphate, 10 gm. per day, seemed to cause a retention of calcium, perhaps a slight increase in nitrogen storage, a reduced loss of phosphorus, and a reduced excretion of sugar, while sodium chlorid, 10 gm. per day, appeared to have an unfavorable influence on nitrogen, phosphorus and calcium balances. In a later paper (1903-4) von Moraczewski published urine analyses from three cases of diabetes mellitus on various diets. The ingestion of tricalcic phosphate was said again to have reduced the sugar excretion.

Erben⁶ in 1907 found a decreased lecithin content of the blood in diabetes mellitus, and large amounts of alkalies and calcium. In a later

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1. Bocker: *Deutsch. Klin.*, 1853, v, 359.

2. Neubauer: *Jour. f. prakt. Chem.*, 1856, lxvii, 64, 83.

3. Toralbo: *Riv. clin. e terap.*, 1889.

4. Von Moraczewski: *Zentralbl. f. inn. Med.*, 1897, xviii, 921.

5. Von Moraczewski: *Ztschr. f. klin. Med.*, 1898, xxxiv, 59.

6. Erben: *Zentralbl. f. inn. Med.*, 1907, xxviii, 1090.

study he found the blood plasma with a normal lecithin content, but the erythrocytes with lecithin content reduced.

Towles⁷ in 1910 found a lime deficiency in diabetes. Von Noorden⁸ found an excretion of calcium, magnesium and phosphorus much in excess of the quantity in the food, and of phosphorus much in excess of that which would accompany the excreted nitrogen in the soft tissues; and concluded that this was due to catabolism of bone. A. R. Mandel and Lusk⁹ in 1904 also found phosphorus elimination excessive in diabetes. Von Noorden cites the work of van Ackeren, showing that the bones atrophy as a whole, though von Noorden is of the opinion that these phenomena are not due simply to the action of an acid. Von Noorden also has shown an increased excretion of purin bodies in such severe diabetes as results in much destruction of tissues. He cites the work of Gaethgens¹⁰ and Kulz,¹¹ showing that the natural parallelism between nitrogen and phosphorus of food and excreta usually exists, except where there is acidosis. Under this latter condition the phosphorus excretion, as previously noted, becomes supernormal in comparison with the nitrogen outgo.

The loss of calcium in diabetic acidosis was shown by some experiments of Gerhardt and Schlesinger.¹² When the daily intake was 0.81 gm. calcium, and the diet was constant, a healthy man excreted 0.62 gm. calcium and a diabetic patient excreted 1.127 gm. calcium. The results obtained by von Limbeck,¹³ Tenbaum¹⁴ and von Moraczewski agree with those of van Ackeren,¹⁵ Gerhardt and Schlesinger. Dengler¹⁶ showed that the administration of calcium, but not of sodium, can stop for some time the loss of calcium in diabetic acidosis.

The work of Gaethgens, whose experiments were performed in 1866 in his student years, in which he makes the assertion that the calcium metabolism of diabetic patients who are not suffering from acidosis is normal, could not be corroborated and should be counted as an erroneous observation.

We wish here from the following observations of various scientists, working in totally different fields of research, to adduce some relation-

7. Towles: *Am. Jour. Med. Sc.*, 1910, cxi, 127.

8. Von Noorden: *Metabolism and Practical Medicine*, 1907, iii, 600.

9. Mandel and Lusk: *Deutsch. Arch. f. klin. Med.*, 1901, lxxxi, 472.

10. Gaethgens: *Dissertation*, Dorpat, 1866.

11. Kulz: *Diabetes Mellitus*, Jena, 1899, p. 430.

12. Gerhardt and Schlesinger: *Exper. Arch.*, 1899, xlii, 83.

13. Von Limbeck: *Ztschr. f. klin. Med.*, 1898, xxxiv, 439.

14. Tenbaum: *Ztschr. f. Biol.*, 1898, xxxiii, 379.

15. Van Ackeren: *Compare von Noorden's Lehrbuch der Pathologie des Stoffwechsels für Aerzte und Studierende*, 1893, p. 416.

16. Dengler: *Compare von Noorden's Metabolism and Practical Medicine*, 1907, iii, 597.

ship existing between calcium metabolism and glycemia and glycosuria. We will consider the question from the following points of view:

(1) Relation of internal secretions to the control of calcium metabolism and carbohydrate metabolism; (2) Nutrition in pregnancy; lime and carbohydrate metabolism; (3) Infectious diseases characterized by derangement in lime metabolism and its effect on the glycemia; (4) Diabetes mellitus: fat metabolism, carbohydrate metabolism and lime requirements; (5) Experimental diabetes and its effect on calcium metabolism.

1. It is known that extirpation of the pancreas (von Mering) induces a marked disturbance in carbohydrate metabolism, with the elimination of large amounts of glucose in the urine. But the carbohydrate metabolism is not the only derangement of metabolism in the body. Falta and Whitney¹⁷ in 1908 investigated the effects of resection of the pancreas in the dog on the lime metabolism, among other observations. They found a very marked increase in the outgo of all constituents, the increase affecting the minerals more than the protein distinction. The output of calcium was markedly increased as will be seen from Table 1.

TABLE 1.—SHOWING THE EFFECT OF PANCREATECTOMY ON THE CALCIUM ELIMINATION IN THE DOG

Condition of Dog (fasting)	Date	CaO in Urine, Gm.
Normal.....	June 5	0.0175
Normal.....	June 6	0.0198
Normal.....	June 7	0.0246
Normal.....	June 8	0.0366
Pancreas removed.....	June 18	0.0124 (in 14 hrs.)
Pancreas removed.....	June 19	0.1522
Pancreas removed.....	June 20	0.0792
Pancreas removed.....	June 21	0.0885

In this case it seems, therefore, that the carbohydrate loss and the derangement in lime metabolism went hand in hand.

In a paper by Underhill and his collaborators we have another evidence of the simultaneous derangement of carbohydrate and calcium metabolism induced by a disturbance of the internal secretions. It is known from the work of McCallum and Voegtlin¹⁸ that after parathyroidectomy there is an increased elimination of lime with a resulting deprivation of this element from the tissues and the blood. This

17. Falta and Whitney: Beitr. z. chem. Phys. u. Path., 1908, xi, 224.

18. McCallum and Voegtlin: Jour. Exper. Med., 1909, xi, 155.

deficiency induces a condition of tetany which can be cured by the administration of calcium lactate, etc. But not only does the resection of the parathyroids induce lime starvation. Underhill¹⁹ and his collaborators found that there was a disturbance in the glycemia of his dogs, and they draw the following conclusions from their work:

(a) Hypoglycemia resulting from thyroparathyroidectomy is neither the cause nor the effect of the accompanying tetany; for although dextrose injections restore blood sugar content to normal, such injections have little influence on tetany. Moreover the condition of hypoglycemia precedes that of tetany. It is therefore suggested that the removal of the thyroid and parathyroids gives rise to two distinct effects, one being manifested upon the blood sugar regulating mechanism, causing hypoglycemia, the other acting upon the nervous system, producing tetany.

(b) Calcium appears to be intimately associated with both effects, for injections of calcium lactate will temporarily restore blood sugar to normal and also abolish tetany for a time.

(c) Calcium may play an important rôle in maintaining the equilibrium of the blood sugar regulating mechanism during normal life.

In the diseases of the pituitary gland, such as acromegaly, "it is remarkable how often it is associated with diabetes mellitus as a complication" (von Noorden²⁰). Sir Edward Schäfer writes as follows on Acromegaly:

There is often glycosuria . . . According to André Levi glycosuria occurs in from 30 to 50 per cent. of cases of acromegaly. As the case advances, it may be replaced by high degrees of sugar tolerance . . . It is interesting to note that in pregnancy also . . . glycosuria not infrequently occurs.†

In acromegaly there is a distinct disturbance of lime metabolism. Rubinraut,²¹ Edsall and Miller,²² Parhon,²³ Medigreceanu and Kristeller,²⁴ von Moraczewski,²⁵ and Bergeim, Stewart and Hawk²⁶ found a calcium retention. On the other hand, Tauszk and Vas²⁷ found an increased excretion of lime. Varying results were obtained by Franchini,²⁸ Schiff²⁹ and Oberndorfer,³⁰ It must be remembered that the

19. Underhill and Blatherwick: Jour. Biol. Chem., 1914, xix, 119.

20. Von Noorden: Metabolism and Practical Medicine, 1907, iii, 565.

21. Rubinraut: Dissertation, Zurich, 1912.

22. Edsall and Miller: Univ. Pennsylvania Med. Bull., 1903, xvi, 143.

23. Parhon: Cited by Medigreceanu and Kristeller.

24. Medigreceanu and Kristeller: Jour. Biol. Chem., 1911, ix, 109.

25. Von Moraczewski: Ztschr. f. klin. Med., 1901, xliii, 336.

26. Bergeim, Stewart and Hawk: Jour. Exper. Med., 1914, xx, 218.

27. Tauszk and Vas: Pest. med.-chir. Presse, 1899, xxxv, 193.

28. Franchini: Biochem. Zentralbl., Ref. 1904, iii, 522.

29. Schiff: Wien. klin. Wchnschr., 1897, xii, 277.

30. Oberndorfer: Ztschr. f. klin. Med., 1908, lxx, 6.

† Schäfer, Sir Edward: An Introduction to the Study of the Endocrine Glands, 1914, p. 66.

cases of acromegaly studied were during different periods of the disease, and that some of them doubtlessly had no complicating glycosuria, so that the conflicting results can be easily explained.

2. Pregnancy is a condition in which marked metabolic changes go on. Hugounenq³¹ studied the retention of minerals by the human fetus. The retention of minerals by the fetus is slight at first, but very active at the end. At birth the infant contains about 100 gm. of salts. During the last three months of gestation the fetus acquires twice as much mineral matter as previously.

It is generally known that calcium is lost by the mother during pregnancy. The results of Ver Eecke,³² Jagerroos,³³ Michel,³⁴ Schkarin,³⁵ Hoffstrom,³⁶ and others demonstrate this fact. Marquis³⁷ found a normal physiologic decalcification in pregnancy, which if varied to excess will develop into an osteomalacic condition. He concludes that the decalcification in pregnancy is probably due to some disturbance in ovarian, suprarenal or similar functioning, with a predisposition afforded by frequently repeated pregnancies and deficiency of lime in the food. This marked loss of lime in the parturient woman induces a disturbance in the carbohydrate metabolism.

Geelmuyden³⁸ comments on the connection between the functioning of the female internal genital organs and carbohydrate metabolism, saying that glycosuria develops regularly in about 10 or 12 per cent. of all pregnancies. Some have encountered it in 40 per cent. Usually lactose is the sugar in the urine in this benign pregnancy glycosuria, but it may be glucose or both. The proportion of sugar in the urine may be so large as to suggest severe diabetes with acidosis. Some differential points are its onset first during the pregnancy, its independence of carbohydrates in the diet, and the absence of polyuria and excessive thirst. Geelmuyden has known instances of these latter symptoms, polyuria, thirst and pruritus, occurring with unmistakable pregnancy glycosuria.

3. There are certain diseases which are characterized by decalcification, as for example in pneumonia and tuberculosis. In tuberculosis the demineralization is so marked that a French school of physicians

31. Hugounenq: *Compt. rend. Soc. de biol.*, 1899, li, 337.

32. Ver Eecke: *Acad. Roy. de Med. de Belgique*, 1900, xv, 1.

33. Jagerroos: *Arch. f. Gynäk.*, 1902, lxxvii, 517.

34. Michel: *L'obstetrique*, 1896, i, 140.

35. Schkarin: *Monatsbl. f. Kinderh.*, 1910, ix, 65.

36. Hoffstrom: *Arch. f. Physiol.*, 1903, xxiii, 326.

37. Marquis: *L'Obstetrique*, 1914, xxx, 561.

38. Geelmuyden: *Norsk Mag. f. Laegevidensk.*, 1914, lxxv, 865.

have recommended lime therapy for tuberculosis (Ferrier,³⁹ Letulle,⁴⁰ Vanini,⁴¹ Piettre,⁴² Kahn.⁴³

Hopkins⁴⁴ has found a constant hyperglycemia in pneumonia, tuberculosis and other conditions, so in these diseases, also, decalcification and decreased carbohydrate tolerance go hand in hand.

4. Lipemia and acidosis, which are such constantly concurring conditions of diabetes mellitus, have a distinct relationship to calcium metabolism.

Klemperer⁴⁵ observed that in diabetic mellitus the blood contains much cholesterol and lecithin, which originate from the subcutaneous fat. The fat of the viscera is unchanged. The lipins enter the blood because of the breakup of the body cells. Once in the blood, they attempt to regenerate the impaired cells. In brief, diabetic lipemia represents a mobilization of the cell lipins to form new cells.

Drennan⁴⁶ drew the following conclusions as to the pathogenesis of diabetic lipemia:

(a) The lipemia of diabetes mellitus is due to the abstraction of calcium salts from the lipid circulating in the blood.

(b) This abstraction is an attempt on the part of nature to neutralize the organic acid which results from the imperfect oxidation of the sugar in the body, fat in the blood being the lesser of the two evils. Fat embolism may result in the lungs, but may exist quite extensively without causing serious symptoms.

In acidosis there is a marked mobilization of lime from the body. All authors agree that the calcium deficiency is marked in cases of increased acid production in the body due to incomplete or improper oxidation of fats.

5. Experimental glycosuria and experimental diabetes can be induced in several ways. It is known that adrenalin, phlorhizin, caffein, etc., will cause glycosuria. Their method of action is not known. In the case of phlorhizin diabetes, the effect, as has been proved by Zuntz, is local on the kidney. In the case of caffein and adrenalin it may be central. In all of these conditions a simultaneous derangement in lime metabolism is present. Salant and Kahn⁴⁷ in 1913 showed that the administration of calcium to rabbits suffering from caffein diabetes caused a cessation of the glycosuria; and if the animal was fortified

39. Ferrier: *Compt. rend. Soc. de biol.*, 1909, xlix, 464.

40. Letulle: *Presse méd.*, 1909, xvii, 212.

41. Vanini: *Bull. d. sci. méd.*, 1908, No. 8.

42. Piettre: *Compt. rend. Acad. d. sc.*, 1909, cxlviii, 954.

43. Kahn: *Biochem. Bull.*, 1912, ii, 87; *Med. Rec.*, New York, 1914, June.

44. Hopkins: *Am. Jour. Med. Sc.*, 1915, cxlix, 115.

45. Klemperer: *Deutsch. med. Wchnschr.*, 1912, October 10.

46. Drennan: *Med. Rec.*, New York, May 7, 1910.

47. Salant and Kahn: *Jour. Pharmacol. and Exper. Therap.*, 1913, v, 535.

with lime before the caffeine administration, the glycosuria was never apparent. Similar results were synchronously reported by workers in Germany on adrenalin and nicotin diabetes. Furthermore, Jacoby and Rosenfeld⁴⁸ have reported that the administration of calcium lactate to dogs has an immediate effect upon phlorhizin diabetes, the excretion of sugar and acetone falling rapidly to almost zero. The decrease in urinary sugar was accompanied by a parallel decrease in the blood sugar. Thus the sugar formation by phlorhizin is hindered by the lime salts.

Substances which abstract lime from the tissues will induce in certain cases a glycosuria. This is true of citrates and tartrates. We have observed that rabbits will often develop glycosuria upon the administration of tartrates.

Bock and Hoffmann observed that they could induce a glycosuria by injecting large quantities of sodium chlorid. Martin Fischer demonstrated that this glycosuria can be arrested by the administration of calcium chlorid solution.

Surgical production of melituria by puncturing the floor of the fourth ventricle or by extirpation of the pancreas will induce, not only a derangement of the carbohydrate metabolism, but also a violent mobilization of the lime salts.

Hagiwara⁴⁹ has recently reported that he found extensive deposition of calcium in the liver of a man who died in diabetic coma. He could not explain this condition. The calcium in the liver was in the form of soap.

The important rôle that calcium plays in the human economy is well discussed by G. Delgado Palacios.⁵⁰ He found that all diabetics suffer from a calcariuria and lipaciduria.

EXPERIMENTAL

The lime metabolism of five diabetic patients was studied.⁵¹ The patients were kept on a Folin diet, no sugar being given, and portions of the mixed diet were taken to the laboratory for analysis. The urine and feces were collected daily and analyzed. The experiments were conducted for nine days. The patients were in the mild stages of diabetes, none of them suffering from any discomfort. There was no acidosis, no ulceration, no pruritus. The glycosuria varied in the different cases from 1.5 to 2.7 per cent.

48. Jacoby and Rosenfeld: *Biochem. Ztschr.*, 1915, lxi, 155.

49. Hagiwara: *Centralbl. f. allg. Path. u. path. Anat.*, 1915, xxvi, 481.

50. Palacios: *Chimie pathologique Tropicale de la Région Atlantique*, Caracas, Venezuela, 1914. *Biochemical Bulletin*, 1916, v, 78.

51. These investigations were conducted in the Beth Israel Hospital Chemical Laboratory, New York City, in collaboration with Jacob Hoffmann. A preliminary report was made in the *Biochemical Bulletin*, 1915, iv, 213.

It was found that the patients on this diet constantly lost lime from their bodies. In certain instances this loss of calcium was marked, in others it was only slight, but the negative calcium balance was definite at all times. Table 2 shows the daily loss of calcium of each patient for a period of nine days.

TABLE 2.—INTAKE AND OUTPUT OF CALCIUM OXID BY DIABETIC PATIENTS *

Case No.		Day								
		1	2	3	4	5	6	7	8	9
1	Intake.....	1.785	1.826	1.941	2.072	1.785	1.907	1.625	1.789	1.847
	Output.....	1.854	1.878	1.977	2.143	1.795	2.044	1.893	1.937	2.094
	Loss.....	0.069	0.052	0.036	0.071	0.011	0.137	0.278	0.148	0.247
2	Intake.....	1.989	1.937	1.874	1.925	2.130	2.107	2.006	1.994	1.895
	Output.....	2.167	2.027	1.948	2.182	2.229	2.234	2.189	2.276	2.227
	Loss.....	0.178	0.090	0.074	0.256	0.099	0.127	0.133	0.282	0.332
3	Intake.....	2.017	2.172	1.987	1.874	1.975	1.981	1.957	1.944	1.927
	Output.....	2.245	2.258	2.187	1.939	2.187	2.110	2.064	2.163	2.126
	Loss.....	0.228	0.186	0.200	0.065	0.212	0.129	0.107	0.219	0.099
4	Intake.....	1.756	1.728	1.925	1.834	1.955	1.974	1.873	1.977	1.926
	Output.....	1.847	1.847	1.976	2.006	2.139	2.177	2.065	2.164	2.165
	Loss.....	0.118	0.119	0.051	0.172	0.184	0.203	0.192	0.187	0.239
5	Intake.....	2.374	2.177	2.250	2.304	2.572	2.714	2.394	2.424	2.342
	Output.....	2.527	2.264	2.376	2.572	2.837	2.907	2.567	2.637	2.561
	Loss.....	0.153	0.087	0.126	0.268	0.265	0.193	0.173	0.213	0.219

* The lime was determined by the McCrudden method.

In a number of cases in another series we endeavored to remedy this lime deficiency and to observe the effect of the lime administration on the glycosuria and the glycemia of the diabetic patients. The method of procedure was as follows:

The patients were kept on a standard diet for a period of three days, during which the urine was collected and the glucose analyzed daily, the amount of glycemia being also determined. On the same diet the patient was injected intravenously with varying amounts of an eighth-molecular solution of calcium chlorid in physiologic saline. The glycosuria and glycemia were then determined to observe the effect of the treatment. We shall describe our results in detail:

CASE 1.—S. D., a German Jewess, aged 40, married, and having four children, all in good health, had a negative family history.

She had had the usual diseases of childhood, but no other illnesses or operations. She had suffered an injury to the left cornea in 1900, which left an

opacity. Otherwise her history was negative. Her habits were regular and normal.

Her present illness dates from 1912, when she weighed 140 pounds, and since which time the patient has been aware of diabetic conditions. She has been losing weight constantly, has had polydipsia and polyuria frequently and also pruritus vulvae. These symptoms existed at the commencement of treatment.

On physical examination her weight was found to be 110 pounds, her general condition fair, but showing evidences of emaciation. Her heart and lungs were negative, liver slightly enlarged, from the sixth intercostal space to three fingers below the free border of the ribs. There was slight epigastric tenderness, but no abdominal masses. The neurologic status was normal. The blood pressure (Tycos) was systolic 145 millimeters of mercury, and diastolic auscultatory 80.

During 1913 the patient had recorded urinalyses of 1.5, 0.3, 4, 2.5, 0.9 and 4 per cent. of sugar in single specimens of urine. No acetone bodies were present.

During 1914 the urine contained 6 and 5 per cent. in twenty-four-hour specimens.

In February, 1915, a twenty-four-hour specimen showed 6 per cent. and in May, 5 per cent.

On May 15, 1915, the patient was put on a constant diet, which was maintained throughout the entire time of observation. The diet consisted of the following ingredients:

Breakfast: Two eggs, one slice of bread and much butter, one glass of tea with cream, water as much as desired. Dinner: Cooked meat with green vegetables, one slice of bread and much butter, cheese or two eggs, whisky one-half ounce, one glass of tea with cream but no sugar. Supper: Meat soup, cooked meat with green vegetables, cheese or two eggs, one slice of bread and much butter, whisky one-half ounce, one glass tea with cream but no sugar.

On May 18 about 5 c.c. of blood were drawn from the medium basilic vein for analysis, and an intravenous injection of 25 c.c. of the calcium solution in normal saline was given. There were no immediate effects, but for several hours the patient felt very weak. The urine was collected, beginning with an empty bladder at the time of injection.

On May 21 there was made an intravenous injection of 30 c.c. of the calcium solution after a few cubic centimeters of the blood had been drawn for examination. There were no immediate effects, except that the blood pressure fell from that previously mentioned to a systolic of 125 and diastolic of 70 millimeters of mercury. For several hours following the injection the patient said she felt weaker than normal.

On May 30 an intravenous injection of 15 c.c. of calcium solution was made after a little blood had been drawn for examination.

On June 16 an intravenous injection of 40 c.c. of calcium solution was made. The patient felt great general discomfort and weakness. The pulse remained unchanged and the patient had no local reaction.

On June 18 an intravenous injection of 45 c.c. of calcium solution was made. The blood pressure fell to systolic 120, diastolic 70 directly after injection.

On June 20 there was made an intravenous injection of 50 c.c. of calcium solution. When 15 c.c. had been injected, patient suddenly flushed, but became very pale as the injection continued. But the pulse remained strong and regular, and patient left the office after several minutes. There occurred a slight local reaction as a result of a few drops which entered subcutaneously, with very severe pain for several hours. This was relieved by a wet dressing.

On June 22 another intravenous injection of 50 c.c. of calcium solution was made. At the outset there was flushing of the face, but this was followed by pallor. The pulse was good, though the patient felt very weak. No immediate effects followed. For several days the patient had localized swelling at the site of the injection. About an hour after the injection the patient had severe

neuralgic pain in the occipital region, with a sense of constriction about the waist.

On June 24 was made an intravenous injection 30 c.c. of calcium solution of which about 15 c.c. were subcutaneous. At the time there was but little pain, but after two hours there developed the brawny condition previously described, which lasted a considerable length of time.

During the period patient was receiving injections the epigastric sensations of oppression were relieved, but on July 13 they returned, and the weakness was quite troublesome.

It is well here to enumerate some of the by effects produced by the injection of the lime solution. The usual effect was a sudden flushing of the face when about 15 c.c. were injected, followed by marked pallor

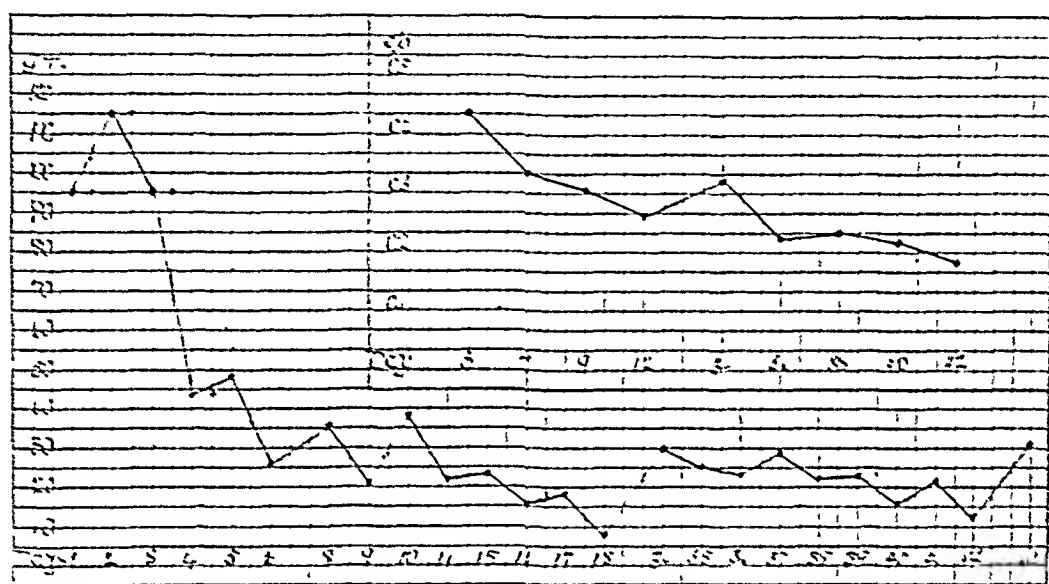


Fig. 1.—The smaller chart shows the fall in hyperglycemia as a result of the calcium solution injections. The vertical column of figures indicates the percentage of blood glucose; the horizontal line the time in days. The larger chart shows the result of the injections on glycosuria. The vertical column of figures indicates the diabetic glucose in grams per day; the horizontal the time in days (S. D., Case 1).

and a feeling of weakness when the injection was continued. After about one hour the weakness in several cases was marked and the patient had to remain in bed for a few hours, complaining of general pains in the muscles. The blood pressure fell immediately after the injection, both systolic and diastolic, with a fall also in the pulse pressure.

In one case, when 15 c.c. of the solution were injected for the first time, the patient said that she "felt hot all over," and then "cold all over," with flushing and pallor respectively, until 30 c.c. were introduced. After thirty minutes the patient felt extremely faint, was pale, had a cold perspiration and for a while was practically unconscious.

She continued in a profuse cold perspiration, and complained of severe aching pain in the arms, chest, back, and legs, and of faintness. The heart sounds were very weak, respiration deep and sighing, marked pallor and cold extremities, with all the signs of collapse. After several hours with hot drink, elevation of the foot of the bed, hot blankets, color and normal general condition returned.

In another instance there was a sensation of fluid "coursing through the brain" for a short period after the injection.

The local effects of subcutaneous extravasation of some of the fluid are at times severe. In one patient in whom 15 c.c. were injected subcutaneously in the right elbow region just beside the vein, there was little pain at the time, but after two hours there occurred marked edema of the anterior aspect of the whole right arm extending from the elbow to the deltoid region. Superficially there appeared red blotches as if the skin were becoming necrosed from pressure. It was freely movable, however, over the very hard and brawny edema. The hardness of the edema was most unusual, as it did not even pit on pressure. At the end of one week the extent of the infiltration began to diminish, but the firmness of consistency of the subcutaneous tissues remained unchanged in the parts still involved. After two more weeks there still was a small area of subcutaneous hardening in the region of the right elbow, which did not pit on pressure and was slightly tender. Finally, however, the arm returned to its normal appearance.

This patient, S. D., was excreting from 95 to 116 gm. of glucose daily. On the third day she was injected with 25 c.c. of calcium solution. The excretion of glucose fell to 43.75 gm. on the fourth day. On the fifth day she excreted 48.60 gm. glucose. She now received another injection of 30 c.c. calcium solution. On the sixth day she excreted 26.83 gm. glucose, and on the seventh day the excretion was 37.92 gm. Again a dose of 30 c.c. calcium solution was administered intravenously. On the day following she had 20.12 gm. glucose, on the ninth day 39.37 gm., on the tenth day 22.60 gm., and on the eleventh day 24.37 gm. glucose. The calcium solution was again injected—15 c.c. On the day following the patient excreted 15.75 gm. glucose, on the thirteenth day 17.87 gm., on the fourteenth day 13.60 gm.

The glycemia was estimated four times, in each case on the blood sample previous to the calcium administration. The hyperglycemia fell from 0.44 per cent. to 0.34 to 0.31 and to 0.27 per cent.

A period of about three weeks was now allowed to elapse from May 30, 1915, to June 16, 1915, when the patient was again treated with the calcium solution. During this time the glycosuria had risen again to 2.6 per cent. and the glycemia to 0.305 per cent. The administration of calcium again had the marked effect of reducing the glycemia and glycosuria.

Table 3 will show the effect of the calcium on the glycosuria and glycemia.

TABLE 3.—EFFECT OF CALCIUM ADMINISTRATION ON THE GLYCOSURIA AND GLYCEMIA OF CASE 1 (S.D.)

Date	Urine, c.c.	Glucose		Glycemia, per Cent.	Remarks
		Per Cent.	Grams		
May 15	1,875	5.1	95.625	
16	2,050	5.7	116.85	
17	2,000	4.8	96.00	0.44	
18	1,750	2.5	43.75	Injection
19	1,800	2.7	48.60	
20	1,720	1.56	26.83	0.34	Injection
22	2,050	1.85	37.92	
23	1,750	1.16	20.12	0.31	Injection
24	1,575	2.5	39.37	
25	1,650	1.4	22.60	
29	1,875	1.3	24.37	0.27	Injection
30	1,750	0.9	15.75	
31	1,625	1.1	17.87	
June 1	1,700	0.8	13.60	
16	1,650	2.5	31.250	0.32	Injection
17	1,500	1.7	25.50	
18	1,625	1.5	24.375	0.22	Injection
19	1,750	1.7	29.750	
20	1,550	1.4	23.700	0.24	Injection
21	1,550	1.4	23.700	
22	1,500	1.1	16.500	0.22	Injection
23	1,875	1.2	22.500	
24	1,650	0.8	13.200	0.19	Injection
July 13	1,750	1.9	33.250	

The acetone "bodies" were never present in the urine.

CASE 2.—S. K., a Russian woman, aged 39, had a family history which was negative for diabetes and tuberculosis.

She had had one curettage, but no illnesses except headaches and fainting sometimes. For two years she had had marked thirst, and one year ago she had been informed that she had diabetes. She had lost much weight despite her good appetite. She had had pruritus vulvae one year, which had become worse recently. Her bowels were constipated.

Physical examination showed her to be in good general condition, weighing 161 pounds. Her heart sounds were clear and normal, and her lungs showed no morbid indications. There was abdominal tenderness in the gallbladder region. The liver and spleen were not palpable. The neurologic status was normal. The blood pressure was systolic 108, diastolic 68.

Sept. 22, 1915, the patient was put on a strict and constant diet which was adhered to throughout the entire period of observation.

On September 25 an intravenous injection of 30 c.c. of the calcium solution was made. The sensation of heat followed by pallor and cold occurred, and the collapse described previously followed in about thirty minutes. The patient received 5 grains of caffeine by mouth at this time, but the urine and blood were examined as usual.

On October 8 she felt much improved, itching was slight, and her weight had increased to 162½ pounds.

On October 25 a sample of blood was taken for examination, but as the cubital veins were very small and deep, the injections were not continued, but the daily administration by mouth of 30 grains of calcium chlorid was begun. On December 3 her weight remained practically unchanged, being 162 pounds.

In this case, following the injection of the calcium solution, the urine sugar and glycemia fell from 5.1 per cent. to 2.7 per cent., and from 0.037 to 0.025, respectively. Her reaction to the lime solution was such that it was deemed inadvisable to continue any intravenous administration in her case.

CASE 3.—C. A. H., a married man, aged 53, referred to us by Dr. Joseph Heine of New York, had a negative family history. His past history showed no illnesses or operations, except that twelve years ago he had an attack of gout in a toe. For the past seventeen years he had drunk about twenty glasses of beer daily. The patient recently has been taking six or seven drinks of whisky, several glasses of claret and several glasses of beer every night between 11 p. m. and 1 a. m., on an empty stomach. He denies venereal disease, and he does not smoke or chew.

For ten years the patient had had diabetes, marked polydipsia and polyuria, but a good appetite. Six years previously he had had sciatic neuritis, following which time he had had slight paresthesias in the feet. At that time the patient had lost 60 pounds in weight. He had had eczema on the legs one year before.

The patient ate at 12 m., then again at 6 p. m. each day. Between 11 p. m. and 1 a. m. regularly each day he drank the great amount of alcohol as mentioned before. The Wassermann test was negative.

Physical examination showed his general condition to be good. He weighed 186 pounds. His heart was regular with no murmurs. The second sounds at the base were not accentuated. The lungs were clear. Superficial band of capillaries quite marked on both sides of chest above the costal margin. The abdomen was protuberant. There were no ascites and no edema of the legs or feet.

Nov. 23, 1915, the patient was put on a constant diet, which was maintained throughout the entire time of observation, and which consisted of the following:

Breakfast: Three eggs, two slices of toast with butter, one whole grapefruit, one glass of tea with cream and saccharin, water ad libitum, sodium bicarbonate one teaspoonful. Dinner: Soup of meat or vegetables, meat, green vegetables, cream cheese, two rolls with butter, one glass of tea with cream. The patient drank seven whiskies daily from 11 p. m. to 1 a. m., and in addition, two glasses of claret and five glasses of beer.

On November 29 was made an intravenous injection of 15 c.c. calcium solution, with no general effects.

On December 2 another intravenous injection of 20 c.c. calcium solution was made, but there was no immediate effects except a sensation of circulation in the head.

December 5 an intravenous injection of 30 c.c. calcium solution was given. The patient at this time weighed 190 pounds.

On December 9 an intravenous injection of 40 c.c. calcium solution was given and on December 12 the patient said he felt much better. Since these injections were given the patient has been on a diet similar to the foregoing, and the urine has gradually diminished to about 70 ounces daily, and has now reached 0.6 per cent. sugar and the patient feels well. The patient's urine is now (May 17, 1916) entirely sugar free.

TABLE 4.—EFFECT OF CALCIUM ADMINISTRATION ON GLYCOSURIA AND GLYCEMIA IN CASE 3 (C. A. H.)

Date	Urine, c.e.	Glucose		Glycemia, per Cent.	Remarks
		Per Cent.	Grams		
Nov. 25	2,875	4.54	130.52	
26	3,025	4.30	130.07	
27	3,275	4.23	128.53	0.427	
29	3,300	2.30	75.90	Injection
30	3,300	2.70	89.10	
Dec. 2	3,300	1.85	61.05	0.235	Injection
3	3,300	1.70	56.10	0.175	Injection
12	2,100	0.6	12.60	

The next several cases will not be reported in such complete detail.

CASE 4.—Mrs. C., who was referred to us by Dr. Zugsmith of Pittsburgh, a woman in easy circumstances, had been suffering from diabetes for a number of years. She was placed on a constant diet and a number of injections of a calcium solution were made. No untoward effects were noticed. The results we obtained in this case are given in Table 5.

TABLE 5.—EFFECT OF CALCIUM ADMINISTRATION ON GLYCOSURIA AND GLYCEMIA IN CASE 4 (MRS. C.)

Date	Urine, c.e.	Glucose		Glycemia, per Cent.	Remarks
		Per Cent.	Grams		
Oct. 6	1,785	3.2	57.12	
7	1,900	3.4	64.60	
8	1,850	1.2	22.20	0.23	Injection
9	1,570	1.4	21.98	
10	1,450	1.1	15.95	
11	1,580	1.7	26.86	
12	1,660	0.9	14.94	0.23	Injection
13	1,655	1.1	18.205	
14	1,470	0.8	11.56	
15	1,750	0.5	8.75	0.21	Injection
16	1,645	0.5	8.225	
17	1,720	0.6	10.32	
18	1,630	0.3	4.89	0.19	Injection
19	1,450	0.2	2.90	
20	1,430	0.8	11.64	
Nov. 18	1,450	1.1	15.95	

CASE 5.—Mr. Y., a patient in the Western Pennsylvania Hospital, was suffering from glycosuria. On a number of days he excreted from 30 to 40 gm. of glucose daily. He received one injection of the calcium solution intravenously. The next day he had no glucose in the urine. He left the hospital at that time, and we do not know the course of the disease since the injection. No untoward effects were observed from the calcium administration.

CASE 6.—Mr. B., a man 53 years of age, had been suffering from diabetes for a number of years. He was treated with calcium administrations. Table 6 shows the result of the intravenous injections of calcium solution.

TABLE 6.—EFFECT OF CALCIUM ADMINISTRATION ON GLYCOSURIA AND GLYCEMIA IN CASE 6 (MR. B.)

Date	Urine, e.c.	Glucose		Glycemia, per Cent.	Remarks
		Per Cent.	Grams		
June 1	2,250	4.7	103.75	
2	2,870	5.2	144.24	
3	2,650	5.1	135.15	
4	2,730	4.8	121.04	
5	1,890	3.4	64.26	0.43	Injection
6	1,850	3.5	64.75	
7	1,780	3.2	56.96	
8	1,920	3.7	71.04	
9	1,670	2.8	46.76	0.41	Injection
10	1,730	2.5	43.25	
11	1,480	2.7	39.96	
12	1,580	2.2	34.76	0.32	Injection
13	1,560	2.4	37.44	
14	1,620	2.5	40.50	
15	1,570	1.7	26.69	0.24	Injection
16	1,540	1.4	21.56	
17	1,790	1.5	25.85	

In a number of cases we endeavored to produce the calcium effect by means of the administration of calcium lactate or chlorid per os. The results that we have obtained are not so striking as those produced by intravenous administration of the calcium. We shall report our results by this method of therapy in a future communication.

In general, we may draw the following conclusions from our experiments:

1. The administration of calcium intravenously to diabetic patients causes a marked fall in the glucose excretion.
2. It induces a gradual decline in the glycemia of the patients.
3. The quantity of urine excreted is reduced.

4. Certain symptoms ascribable to the diabetes are relieved by this treatment.

5. Acetone, diacetic acid and beta-oxybutyric acid never developed in these cases.

We are continuing our work along these lines.

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FURTHER STUDIES IN THE INACTIVATION OF PEPSIN

THE EFFECTS OF VARIOUS SALTS AND ALKALINE SUBSTANCES *

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In a previous communication by one of us¹ it was demonstrated that sodium chlorid will prevent pepsin in aqueous solution from digesting protein. It was further pointed out that the inhibition of pepsin by sodium chlorid is permanent, that is, the subsequent addition of hydrochloric acid fails to reactivate the ferment. This phenomenon of pepsin inhibition may be prevented by dissolving the ferment in dilute hydrochloric acid.

The inactivation of pepsin by sodium chlorid suggested the desirability of studying the action of various other salts to ascertain, if possible, whether this phenomenon was specific or whether it was common to many salts. Before this was attempted, however, a somewhat more detailed quantitative study of the action of sodium chlorid itself was made. The results from this study are shown in Table 1. Here it was found that the inhibitory effect of sodium chlorid is a quantitative reaction, that is, inhibition diminishes with the concentration of salt present. For instance, a concentration of 2.5 per cent. causes practically complete inhibition of pepsin. Lesser concentrations cause only partial inhibition, while concentrations of less than 0.25 per cent. cause practically no inhibition at all. In fact, in concentrations of salt below 0.25 per cent. inhibition is not only absent but is supplanted by actual acceleration, that is, there is apparently an optimum concentration of sodium chlorid of about 0.1 per cent., at which point peptic digestion is greater than in the entire absence of salt.

Similar studies were made with various chlorids, namely, potassium, barium, strontium, ammonium, magnesium and iron. The results with these salts were all practically the same, the phenomenon of inhibition remaining a quantitative reaction with evidence of acceleration in high dilutions.

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* Read at the Eighth Annual Meeting of the American Society for the Advancement of Clinical Investigation, Washington, D. C., May 8, 1916.

1. Hamburger: THE ARCHIVES INT. MED., 1915, xvi, 356.

In connection with the inhibiting effect of these various chlorids the thought was suggested that hydrochloric acid itself might have an inhibiting action at certain concentrations. We made, therefore, quantitative studies with varying strengths of hydrochloric acid, with results as shown in Table 2. Here it may be seen that hydrochloric acid in concentrations of from 0.7 to 0.9 per cent. causes almost complete inhi-

TABLE 1.—QUANTITATIVE INHIBITION OF PEPSIN BY SODIUM CHLORID*

Tube	Pepsin in H ₂ O, 1 to 300,	5 per Cent. NaCl	Normal HCl	H ₂ O	Digestion	
					24 Hr.	44 Hr.
1	5 c.c.	5 c.c.	0.5 c.c.	0	0	Trace
2	5 c.c.	1 c.c.	0.5 c.c.	4	+	++
3	5 c.c.	0.5 c.c.	0.5 c.c.	4.5	+	++
4	5 c.c.	0.1 c.c.	0.5 c.c.	4.9	++	+++
5	5 c.c.	0 c.c.	0.5 c.c.	5	++	++++

* Sodium chlorid in high concentrations (2.5 per cent.) causes complete inhibition of pepsin dissolved in water (Tube 1). In less concentrations inhibition, while not complete, is still present as compared with control (Tube 5). In concentrations less than 0.25 per cent. (Tube 4) the inhibition is almost negligible.

TABLE 2.—INHIBITION AND ACCELERATION OF PEPSIN BY HYDROCHLORIC ACID*

Tube	Pepsin in H ₂ O, 1 to 500	Normal HCl	H ₂ O	Digestion 48 Hr.
1	4 c.c.	2 c.c.	2 c.c.	0
2	4 c.c.	1.5 c.c.	2.5 c.c.	Trace
3	4 c.c.	1 c.c.	3 c.c.	+
4	4 c.c.	0.75 c.c.	3.25 c.c.	+
5	4 c.c.	0.5 c.c.	3.5 c.c.	++
6	4 c.c.	0.25 c.c.	3.75 c.c.	+++
7	4 c.c.	0.1 c.c.	3.9 c.c.	++
8	4 c.c.	0.05 c.c.	3.95 c.c.	+
9	4 c.c.	0 c.c.	4 c.c.	0

* Hydrochloric acid in high concentrations (0.7 to 0.9 per cent.) inhibits peptic digestion almost entirely (Tubes 1 and 2). Concentrations of about 0.1 per cent. (Tube 6) is optimum concentration under given conditions; in lesser concentrations, digestion again diminishes.

bition of aqueous pepsin. We found, further, that there was an optimum concentration of 0.1 per cent. at which point peptic digestion is at its height under given conditions, while in lesser concentrations down to entire absence of acid, digestion is proportionately less. In other words, we found evidence of a quantitative chemical reaction with a changing curve of peptic digestion reaching its maximum at a definite point under given conditions of optimum concentration.

Inasmuch as our work thus far had shown the equality of the various chlorids tested, we determined to vary the acid portion of the salt, the metal portion remaining constant. We chose for investigation the acetate, the citrate, the phosphate, and the carbonate of sodium. The results from this series were extremely interesting, for while the citrate and acetate showed practically the same results as the chlorids, the phosphate and carbonate showed a much greater inhibition. Table 3 contains a quantitative study of sodium phosphate, showing complete inhibition of pepsin in dilutions up to 1 to 200 and partial inhibition in

TABLE 3.—INHIBITION OF PEPSIN BY SODIUM PHOSPHATE*

Tube	Pepsin in H ₂ O, 1 to 1,000	5 per Cent. Na ₂ HPO ₄	Normal HCl	H ₂ O	Digestion		
					22 Hr.	46 Hr.	70 Hr.
1	5 c.c.	5 c.c.	0.5 c.c.	0	0	0	0
2	5 c.c.	4 c.c.	0.5 c.c.	1	0	0	0
3	5 c.c.	3 c.c.	0.5 c.c.	2	0	0	0
4	5 c.c.	2 c.c.	0.5 c.c.	3	0	0	0
5	5 c.c.	1 c.c.	0.5 c.c.	4	0	0	0
6	5 c.c.	0.8 c.c.	0.5 c.c.	4.2	0	Trace	Trace
7	5 c.c.	0.6 c.c.	0.5 c.c.	4.4	0	Trace	Trace
8	5 c.c.	0.4 c.c.	0.5 c.c.	4.6	0	Trace	+
9	5 c.c.	0.2 c.c.	0.5 c.c.	4.8	Trace	+	++
10	5 c.c.	0.1 c.c.	0.5 c.c.	4.9	+	++	+++
11	5 c.c.	0	0.5 c.c.	5	++	+++	++++
12	5 c.c.	5 c.c. NaCl	0.5 c.c.	0	0	Trace	+
13	5 c.c.	1 c.c. NaCl	0.5 c.c.	4	+	++	++
14	5 c.c.	5 c.c. NaC ₂ H ₃ O ₂	0.5 c.c.	0	0	Trace	Trace
15	5 c.c.	1 c.c. NaC ₂ H ₃ O ₂	0.5 c.c.	4	++	+++	+++

* Sodium phosphate in dilutions up to 1 to 200 (Tube 5) causes complete inhibition of peptic digestion. In higher dilutions up to 1 to 2,000 (Tube 10) produce partial inhibition, as compared with control (Tube 11). Inhibition of other sodium salts (chlorid and acetates) in the same dilution was practically absent (Tubes 13 and 15).

dilutions as high as 1 to 2,000. This inhibition in high dilutions is in marked contrast to the results obtained with the sodium chlorid, for complete inhibition could be demonstrated only in dilutions up to 1 to 40 and partial inhibition in 1 to 400. In other words, the inhibiting effect of the phosphate may be said to be five times that of the chlorid, acetate or citrate.

A variety of inorganic and organic salts and alkaline substances were now tested under similar conditions, either on aqueous pepsin or on gastric juice. In the studies on gastric juice we would emphasize that a new and important factor enters into the reaction, namely, the

hydrochloric acid of the gastric juice, for in all of the work thus far the inactivating action of the various salts was tested on aqueous pepsin, which, as was shown in the earlier work, could be entirely protected by the addition, first, of hydrochloric acid.

Table 4 shows the results of the action of a series of salts on pure gastric juice. The results from this table may be said in brief to be entirely a question of the neutralization of the hydrochloric acid of the juice and the ability of the various salts and alkaline substances to

TABLE 4.—EFFECT OF VARIOUS SALTS AND ALKALINE SUBSTANCES ON GASTRIC JUICE*

Tube	1st Addition	2d Addition	3d Addition, Normal HCl	Digestion	
				24 Hr.	48 Hr.
1	1 c.c. gastric juice	1 c.c. 5% Na_2CO_3	5 c.c.	0	0
2	1 c.c. gastric juice	5 c.c. 5% Na_2CO_3	5 c.c.	0	0
3	1 c.c. gastric juice	1 c.c. 5% $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$..	5 c.c.	+	++
4	1 c.c. gastric juice	0.5 c.c. 5% $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$	5 c.c.	++	+++
5	1 c.c. gastric juice.	1 c.c. 5% Na_2HPO_4	5 c.c.	+	++
6	1 c.c. gastric juice	0.5 c.c. 5% Na_2HPO_4 ...	5 c.c.	++	++++
7	1 c.c. gastric juice	1 c.c. 5% $\text{Mg}(\text{OH})_2$	5 c.c.	+	++
8	1 c.c. gastric juice	0.5 c.c. 5% $\text{Mg}(\text{OH})_2$...	5 c.c.	++	++++
9	1 c.c. gastric juice	1 c.c. 5% MgCO_3	5 c.c.	0	0
10	1 c.c. gastric juice	0.5 c.c. 5% MgCO_3	5 c.c.	+	+
11	1 c.c. gastric juice	1 c.c. 5% KI	5 c.c.	Trace	+
12	1 c.c. gastric juice	0.5 c.c. 5% KI	5 c.c.	+	++
13	1 c.c. gastric juice	1 c.c. 5% $\text{NaC}_2\text{H}_4\text{NO}_6$	5 c.c.	Trace	++
14	1 c.c. gastric juice	0.5 c.c. 5% $\text{NaC}_2\text{H}_4\text{NO}_6$	5 c.c.	+	+++
15	1 c.c. gastric juice	1 c.c. 5% FeCl_3	5 c.c.	+	+
16	1 c.c. gastric juice	0.5 c.c. 5% FeCl_3	5 c.c.	+	+
17	1 c.c. gastric juice	Control.....	5 c.c.	++	++++

* Carbonates show most striking inhibition, sodium carbonate more than magnesium carbonate. The inhibition is probably due to the alkalinity and the ability to neutralize the free hydrochloric acid of the gastric juice.

cause complete or partial neutralization. From this view point, as was to be expected, the carbonates showed by far the greatest inhibiting action, the sodium carbonate more than the magnesium. From triple tests with each salt, three indicators being used, namely, phenolphthalein, methyl orange and dimethylamido-azobenzol, it could be demonstrated that in the tubes showing complete inhibition the degree of alkalization had progressed the farthest. We conclude, therefore, that sodium carbonate is of maximum value among the salts used for producing complete neutralization or alkalization of gastric juice.

Confirmatory evidence of this view may be found in the results obtained in Table 5. Here it may be seen that when only free hydrochloric acid is neutralized, and then subsequently activating hydrochloric acid added, peptic digestion is simply reduced; however, when total acidity is neutralized and subsequently activating hydrochloric acid added, peptic digestion is destroyed completely and permanently.

These results, therefore, show that in order to control peptic digestion completely and permanently, total acid must be completely neutralized; for if only *free* acid is neutralized peptic digestion is prevented only temporarily (during the period of such neutralization), inasmuch as the subsequent addition of hydrochloric acid suffices to reactivate a considerable portion of the ferment. Of course, if the neutralization of free acid can be maintained, which means, clinically, the neutralization of all free acid as soon as secreted, peptic digestion will be controlled entirely during this period.

TABLE 5.—EFFECTS OF PARTIAL AND COMPLETE NEUTRALIZATION OF GASTRIC JUICE*

Tube	1st Addition	2d Addition	3d Addition	Digestion
1	3 c.c. gastric juice	N/10 NaOH sufficient to neutralize free HCl	0
2	3 c.c. gastric juice	N/10 NaOH sufficient to neutralize free HCl	N/10 HCl sufficient for peptic digestion	++
3	3 c.c. gastric juice	N/10 NaOH sufficient to neutralize total acidity	0
4	3 c.c. gastric juice	N/10 NaOH sufficient to neutralize total acidity	N/10 HCl sufficient for peptic digestion	0
5	3 c.c. gastric juice	Control.....	++++

* Neutralization of free acid only (Tube 2) does not completely destroy peptic activity. Neutralization however of total acidity (Tube 4) destroys pepsin completely and permanently.

COMMENT

Summarizing the results which this study has brought forth, we may say that the inactivation of pepsin by sodium chlorid is not a specific phenomenon, but may be duplicated by any of a series of inorganic and organic salts. Further, the phenomenon partakes of the nature of a quantitative reaction, higher concentrations causing complete inhibition, lesser concentrations causing partial inhibition, while minimal concentrations cause acceleration. Hydrochloric acid also may act as an inhibiting agent to pepsin, in concentrations varying between 0.7 and 0.9 per cent. Such concentrations are considerably higher than are present in human gastric juice and are considerably higher than the concentration of salts causing pepsin inactivation.

Carl Oppenheimer and others previously have called attention to the inhibition or destruction of pepsin by relatively strong concentrations of hydrochloric acid. With the exception of such strong alkalies as sodium carbonate, sodium hydroxid, magnesium carbonate and calcium hydroxid, sodium phosphate causes the inactivation of aqueous pepsin in dilutions far greater than any salt investigated. Sodium phosphate inhibits or destroys pepsin in dilution five times greater than that of sodium chlorid, sodium acetate or sodium citrate. While this inactivation of pepsin by sodium phosphates suggests the possibility of a specific action, it is likely that this result is due to the feeble alkalinity exhibited by this salt. As Langley pointed out originally, alkalies, such as sodium carbonate, sodium hydroxid, magnesium carbonate and calcium hydroxid, inhibit pepsin by virtue of their alkalinity (hydroxyl ion concentration). We believe that our results are to be explained by this same chemical reaction. Langley found that pepsin was extremely sensitive to alkalies. He pointed out that if one wishes to neutralize gastric juice without destroying the activity of most of the pepsin, one should add calcium carbonate and then a very weak alkali, such as sodium acetate or milk of lime.² We believe it probable, therefore, that the inhibition of pepsin, both by salts and alkaline substances, is one and the same phenomenon, namely, the phenomenon of hydroxyl ion concentration, causing inhibition.

From a clinical point of view the results from this work suggest, theoretically at least, the advisability of using sodium chlorid and sodium phosphate in addition to the usual alkaline substances in the treatment of diseases of the stomach in which the control of peptic digestion may be desired. Whether or not the addition of sodium chlorid and sodium phosphate will actually aid in such therapy can only be determined by the clinical use of these salts in a considerable number of cases. Likewise the problem of the amounts required to control peptic digestion will necessitate prolonged clinical usage. In this respect, of course, the laxative effect of large amounts of sodium phosphate must be taken into consideration, as well as any possible remote (kidney) effects of large amounts of sodium chlorid. At the present time such clinical studies are being made. At this time we wish merely to call attention to their use and to suggest that as a prophylactic measure to aid in the prevention of gastric and duodenal ulcer, as well as a therapeutic agent to promote the healing of chronic ulcer, sodium chlorid and sodium phosphate should be used in addition to the usually employed alkaline drug and dietary treatment. It may be further suggested that inasmuch as sodium carbonate, magnesium carbonate and calcium hydroxid offer the maximum neutralizing value, these substances be used in place or in addition to the alkalies usually used in gastro-intestinal therapy.

2. Quoted from Mathews' Text-Book of Physiological Chemistry.

CONCLUSIONS

1. The inactivation of pepsin by sodium chlorid is not a specific phenomenon, but may be duplicated by any of a series of inorganic and organic salts.

2. The inactivation of pepsin by sodium chlorid is a quantitative chemical reaction. Concentrations of 2.5 per cent. cause complete inhibition; concentrations of 0.25 per cent. cause little, if any, inhibition; concentrations of 0.1 per cent. cause acceleration.

3. Hydrochloric acid in concentrations from 0.7 to 0.9 per cent. acts as an inhibiting agent to pepsin.

4. Sodium phosphate in dilutions of 1 to 200 causes complete inhibition of pepsin and in dilutions of 1 to 2,000 it causes partial inhibition of pepsin. The inhibition of sodium phosphate may be said to be five times that of sodium chlorid and of most inorganic and organic salts, with the exception of the strong alkalies.

5. The inhibition of pepsin by various salts and alkaline substances is probably due to the hydroxyl ion concentration of the solutions used.

6. The inhibition of pepsin by sodium chlorid and sodium phosphate suggests the possibility of the clinical use of these salts in the prevention and cure of chronic gastric ulcer.

7. The strong neutralizing value of sodium carbonate, magnesium carbonate and calcium hydroxid suggests the possibility of their use under similar conditions.

THE RATE OF ABSORPTION OF VARIOUS DIGITALIS PREPARATIONS FROM THE GASTRO-INTESTINAL TRACT *

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It has been shown that alcohol present in the tincture of digitalis delays the absorption of the active principles when this preparation is injected subcutaneously into guinea-pigs.¹ It seemed possible that the same delay in absorption might occur when the tincture was given orally, and this possibility is strengthened by the observations of Ryan,² who found that the absorption of strychnin from the stomach was delayed by the presence of alcohol, and those of Sollmann,³ showing that alcohol delays the absorption of phenol from the alimentary tract. This is a point of some practical importance, for the delay in absorption not only delays the beginning of the desired digitalis action, but also allows a longer time for the digestive juices to act on the glucosids, causing, according to Hale,⁴ more or less destruction of these latter.

Obviously, the most satisfactory way to determine the rate of absorption of a drug from the alimentary tract is to note the lapse of time between the oral administration of the drug in question and the appearance of definite symptoms which must be attributed to this drug. In investigating the rate of absorption of several digitalis preparations Cow⁵ employed a method based on this principle. He used decerebrate cats, but instead of introducing the drug into the stomach, he injected it into the lumen of the small intestine and observed any subsequent change in the blood pressure. It would seem that there are two objections that can be advanced against this: first, the animals were deeply anesthetized, to be then operated on; and, second, the drug did not pass through the stomach, and this might have a decided influence on the results. Gottlieb⁶ investigating the rate of absorption

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* From the Department of Pharmacology, Medical College of Virginia, Richmond, Va.

1. Haskell: *Jour. Am. Pharm. Assn.*, 1913, ii, 836.

2. Ryan: *Jour. Pharmacol. and Exper. Therap.*, 1912-1913, iv, 43.

3. Sollmann, Hanzlik and Pilcher: *Jour. Pharmacol. and Exper. Therap.*, 1909-1910, i, 409.

4. Hale: *Jour. Am. Med. Assn.*, 1911, lvii, 1515.

5. Cow: *Biochem. Jour.*, 1911-1912, vi, 219.

6. Gottlieb and Ogawa: *München. med. Wchnschr.*, 1912, lix, 2265.

of digipuratum and of powdered digitalis leaf, placed the preparations in the small intestine, and after the lapse of a given length of time, determined the amount of digitoxin remaining. The same objection might be urged against this injection site as was brought forward in regard to Cow's experiments, and, in addition, it is not generally believed that the determination of the so-called digitoxin by Keller's method is a procedure to be relied on.

In our first experiments the attempt was made to secure evidence of absorption after the oral administration of digitalis to anesthetized dogs, a constant record of carotid blood pressure being taken over periods of several hours. Irrespective of the digitalis preparation used, however, or the size of the dose, no evidence of absorption could be seen, even when the observations were continued over three hours.

It has been shown by Hatcher⁷ that the seat of the emetic action of digitalis is central and not due to local irritation of the stomach. Therefore, emesis after the oral administration of a digitalis preparation indicates that absorption has occurred. Bearing this in mind, we gave a series of cats digitalis leaf, or infusion or tincture made from this leaf. The leaf was used in the form of a No. 60 powder; the tincture was made according to the official method. The infusion was made by placing the powdered leaf in a flask and adding boiling water in the proportion of about 90 c.c. for each 3 gm. of leaf. The flask was wrapped up and, in the first experiments, allowed to stand exactly three hours, in the later experiments, exactly four hours. The contents of the flask were then poured on a cloth filter, the leaf pressed, and water added through the filter until the finished infusion represented thirty grams of leaf to the liter. The tincture was tested on frogs and guinea-pigs at the time of its percolation, and each sample of infusion was tested in the same manner when made. No infusion over twenty-four hours old was used. Tincture and infusion assayed alike by the two methods.

All the animals received the drug by mouth. The powdered leaf was suspended in tap water and washed down with a small amount of water; the tincture was given as such, and was washed down with about an equal amount of water, except in three instances, in which the alcohol was evaporated off. The infusion was administered in an unchanged form. The results of these experiments are given in Table 1.

The result of these experiments would indicate that the infusion is absorbed more slowly than is the tincture. The experiments with the leaf are too few in number to permit of drawing conclusions for that preparation. When a dose of the infusion corresponding to 400 mg.

7. Hatcher and Eggleston: *Jour. Pharmacol. and Exper. Therap.*, 1912-1913, iv, 113.

of leaf per kilogram cat was given to two cats, the average lapse of time before emesis was 267 minutes; when a similar dose of tincture was given to three other cats, the average lapse of time was 36.3 minutes. When the infusion dose was increased to 600 mg., 136.5 minutes elapsed as the average of two cats; while, with a corresponding dose of the tincture, one cat succumbed to the poisoning in 91 minutes without vomiting, the other vomited in 32 minutes after receiving the drug. A dose of the tincture corresponding to 300 mg. of leaf administered to two cats caused emesis in the average time of 37.5 minutes.

TABLE 1.—EFFECT OF DIGITALIS PREPARATIONS ADMINISTERED TO CATS

Preparation	Mg. Leaf per Kg. Cat	Time Before Emesis, Min.
Leaf.....	100	27
Leaf.....	300	78
Leaf.....	300	71
Infusion.....	200	No emesis
Infusion.....	300	175
Infusion.....	400	203
Infusion.....	400	331
Infusion.....	500	53
Infusion.....	600	150
Infusion.....	600	123
Tincture.....	100	55
Tincture.....	200	13
Tincture.....	300	18
Tincture.....	300	57
Tincture.....	400	26
Tincture.....	400	40
Tincture.....	400	43
Tincture.....	500	12
Tincture.....	600	32
Tincture.....	600*	...

* Death in 91 minutes without emesis.

The rate of absorption of various digitalis bodies from the gastrointestinal tract has been investigated in Hatcher's laboratory,⁸ and it seemed desirable that the results given in Table 1 should be verified by the procedure that Hatcher has found so suitable for studying the rate of absorption from the alimentary tract of lower animals. This method is carried out on cats, a definite dose of the drug being given by mouth, and after the lapse of a suitable length of time a solution

8. Hatcher and Eggleston: Jour. Am. Med. Assn., 1914. lxiii, 468, 469.

of the same or a similar drug is gradually injected intravenously until the death of the animal occurs. Since the lethal dose for cats can be quite accurately determined with the digitalis bodies, it is obvious that the difference between the average lethal dose of the preparation in question and that actually required to kill an animal that has previously received an oral dose represents the amount of drug that has been absorbed from the stomach or intestines.

In carrying out our experiments according to this method, a tincture was made from digitalis leaf according to the official process, save that a No. 40 powder was used. This tincture was placed in a cork-stoppered pint amber bottle and used throughout the experiments, no assay being made after the original test, when it was found that a dose of this tincture corresponding to 100 mg. per kilogram cat was required to cause the death of the animals. The infusion was also made from the leaf in the form of a No. 40 powder. It was found, on using the process previously described, except that the water and leaf were allowed to remain in contact for exactly one hour, the finished infusion representing 20 gm. of the leaf to the liter, or, in other words, a 2 per cent. infusion, that infusion and tincture were of the same strength, figured on the basis of leaf represented. That is, 5 c.c. of a 2 per cent. infusion possessed the same amount of toxicity for cats as 1 c.c. of the 10 per cent. tincture. Hatcher and Eggleston⁹ have recently shown that even the infusion does not deteriorate very rapidly, but it was deemed safer to use no infusion over twenty-four hours old.

The question arises as to the amount of absorption after the cats have been etherized. Necessarily, a considerable amount of time is taken up with the operative procedures and with the gradual intravenous injection. It has already been pointed out that dogs anesthetized with morphin-ether do not seem to absorb digitalis administered orally, and it is possible that with cats also absorption is largely inhibited after the induction of ether anesthesia. After placing the animals on the board and inserting the vein cannula, the attempt was made to avoid the further use of ether, but it was found that a small amount was required to keep the animals quiet. Frequently, the cats vomited, and if this occurred soon after the administration of the drug, it doubtless served to remove a portion of the dose that otherwise would have been absorbed and would have contributed to the lethal effect. In view of these facts, note was made of the time of oral administration, time of beginning ether, occurrence of emesis, and time of death. Some of the cats were starved twenty-four hours before use, others were allowed food, so the presence or absence of food in the stomach is also recorded. The results of these experiments are given in Table 2.

9. Hatcher and Eggleston: Jour. Am. Med. Assn., 1915, lxxv, 1902.

TABLE 2.—ABSORPTION OF TINCTURE AND INFUSION BY CATS

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
Infusion:							
F.	2,300	100	42	0	117	Empty	1.3
M.	2,100	100	49	0	116	Food	4.5
F.	1,700	300	42	0	110	Food	10.8
M.	3,200	200	29	0	102	Empty	8.5
M.	3,300	300	31	50	132	Empty	0
M.	3,560	300	26	71	144	Empty	0
F.	1,660	300	24	66	142	Food	0
M.	2,570	300	28	97	102	Empty	0
F.	1,950	300	32	0	97	Empty	0
F.	1,265	300	20	40	90	Empty	0
M.	3,200	300	196	223	225	Food	9.8
F.	1,925	300	182	240	268	Food	3.0
Tincture:							
M.	2,370	300	25	57	130	Food	25
F.	2,430	300	22	65	87	Empty	12.6
F.	2,610	300	28	66	118	Empty	12.9
M.	3,175	300	30	75	140	Empty	15.0
M.	2,790	300	24	102	103	Empty	13.6
M.	1,810	400	16	0	73	Food	0
M.	2,210	400	20	33	82	Food	2.4
F.	2,500	400	54	41	142	Empty	7.8
M.	3,180	400	40	38	75	Empty	8.2
F.	2,610	400	28	66	118	Empty	9.7
M.	2,790	400	24	103	103	Empty	10.2
M.	3,175	400	30	75	140	Empty	10.8
F.	3,400	400	21	16	86	Empty	11.3
F.	2,763	400	20	0	140	Empty	12.8
F.	1,310	400	20	0	94	Empty	13.7

It is evident from Table 2, that here also the rate of absorption of the tincture is much more rapid than is the case with the infusion. Six animals with empty stomachs received a dose of infusion equivalent to 300 mg. of leaf per kilogram of body weight, and after an average lapse of 111 minutes, only a little more than 1 per cent. of the dose administered was absorbed. Four cats with empty stomachs received a similar dose of tincture, and after the lapse of 112 minutes as an average, it is seen that over 13 per cent. of the dose had been absorbed. When the dose of tincture was increased to 400 mg., the percentage of absorption decreased somewhat, falling to about 9 per cent. As the

result of all the infusion experiments, an average absorption of 3.2 per cent. occurred; as the result of all the tincture experiments, an average of 9.5 per cent. The average lapse of time for the infusion animals was 137 minutes; for the tincture animals, 109 minutes.

It has been found that it is the presence of alcohol that delays absorption of digitalis after subcutaneous administration. Could it be that the alcohol had the reverse effect when the preparation is administered orally, or is the more rapid absorption of the tincture from the alimentary tract to be explained by the fact that it is a more concentrated preparation? In order to determine whether either of these factors exerted an influence, a portion of the tincture was evaporated on a water bath to a semisolid consistency and then suspended in tap-water to make a 2 per cent. solution, being, therefore, free from alcohol and having the same bulk as the infusion. This modified preparation was given to four cats with the results as shown in Table 3.

TABLE 3.—ABSORPTION OF AQUEOUS SUSPENSION OF TINCTURE
RESIDUE BY CATS

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
M.	2,370	300	25	57	130	Food	2.3
F.	2,430	300	22	65	87	Empty	12.6
F.	26,100	300	28	66	118	Empty	12.9
M.	3,175	300	30	75	140	Empty	15

From these four experiments it is seen that the removal of the alcohol from the tincture and the increase in the bulk of the fluid has no influence on the rate of absorption. The average absorption was 10.9 per cent. of the administered dose, as against 9.5 per cent. in the series of animals receiving the ordinary alcoholic tincture. It would seem, therefore, that some constituent present in the infusion inhibits to a certain extent the absorption from the gastrointestinal tract of cats. Whether this occurs in man to an extent sufficient to play an important rôle is to be determined by clinical experimentation. From his clinical observations Eggleston¹⁰ concludes that there is little or no difference in the action of the infusion and the tincture, but possibly more careful attention to the rate of absorption may reveal differences of considerable degree.

There are several special digitalis preparations on the market, possessing, according to the claims of their exploiters, numerous advantages over the galenical preparations. It has been shown that many

10. Eggleston: THE ARCHIVES INT. MED., 1915, xvi, 1.

of these claims arise rather from a pleasing optimism of the manufacturers than from the ground of experimental fact, and, taking everything into consideration, we can see but few, if any, reasons for preferring them to the official preparations of suitable strength. Among other claims, it has been stated that some of these special preparations are more readily absorbed than are the official preparations. Aside from the experiments of Gottlieb that have already been mentioned, it does not seem that this question has been investigated by the exploiters of these preparations. To determine whether the rate of absorption really differed from that of the official preparations, samples of digipuratum, digalen, and digipoten were secured either from jobbers or retail druggists. These samples were first assayed by the cat method, and the rate of absorption after oral administration to cats was determined as in the preceding experiments.

The sample of digipuratum assayed by the cat method was found to possess a high degree of activity, the average lethal dose being 88 mg. per kilogram body weight. The tincture made in the laboratory from selected leaf and used in the preceding experiments, assayed in the same way, required a dose equivalent to 100 mg. leaf per kilogram body weight. The digalen sample was found much inferior in strength, the average dose being 428 mg. per kilogram. It is evident that this preparation is much weaker than a good sample of tincture, which is in agreement with previous assays of digalen by Hale¹¹ and by Hatcher.¹² The sample of digipoten also seemed of good strength, the lethal dose being 91 mg. per kilogram body weight. It was noticed, however, with this last preparation, that the death of most of the cats was atypical. A single blood pressure and respiration record was taken from a dog being poisoned with digipoten, and it was found that a gradual rise of pressure and slowing of the heart beat occurred, while the respiration, first stimulated in a decided manner and then depressed, continued a short while after the pressure had fallen to zero and the heart beat could no longer be detected. Apparently the preparation possesses the true digitalis action, but, from the manner of death of the cats, it would be necessary to investigate this more fully.

The results with digipuratum are given in Table 4.

It is plainly evident from these six experiments that digipuratum is absorbed less rapidly than is the tincture. When the dose of 300 mg. per kilogram body weight was given orally to six cats, at the end of an average of 161 minutes, an average absorption of about 5 per cent. of this dose had occurred; while with a similar dose of the tincture, after the lapse of an average of 112 minutes, an average absorption of about 13 per cent. had occurred. The sample of digipuratum is some-

11. Hale: Bull. Hyg. Lab., U. S. P. H. S., No. 74.

12. Hatcher: Jour. Am. Med. Assn., lviii, 921.

what stronger than was the tincture, but this does not nearly compensate for the difference in the rate of absorption.

TABLE 4.—ABSORPTION OF DIGIPURATUM BY CATS

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
F.	2,720	300	47	0	149	Empty	13.7
M.	4,155	300	37	82	187	Empty	4
F.	3,270	300	33	98	151	Empty	5.6
F.	2,334	350	36	0	161	Empty	1
F.	3,025	300	30	90	152	Empty	1
M.	2,490	300	85	0	166	Empty	5.3

The results secured in the experiments with digalen are given in Table 5.

TABLE 5.—ABSORPTION OF DIGALEN BY CATS

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
F.	1,425	300	59	0	111	Empty	42.8
M.	1,725	300	62	55	135	Empty	35.6
F.	1,275	300	33	58	98	Empty	21.4

From these three experiments, it would seem that digalen is absorbed much more rapidly than either the tincture or digipuratum. That this means that digalen is to be preferred to the other preparation is by no means the case. While, as the average, the absorption of digalen in 114 minutes was about 33 per cent. of the dose administered, this in reality amounted to only about 8 per cent. of the tincture. So, at the end of the stated time, active principles had been absorbed from the digalen dose to amount to about 8 per cent. of the tincture, while, the tincture itself being given, the absorption amounted to 13 per cent.

It does not seem out of place to mention the relative cost of these preparations. We have recently had occasion to purchase a number of four ounce samples of physiologically tested tincture of digitalis from the local retailers, and the price was uniformly 40 cents, or at the rate of 10 cents an ounce. Digipuratum, in the form of tablets, retails in Richmond at 90 cents for twelve tablets, each tablet, according to our assays, being equivalent to a little less than 16 minims of a good tincture. Digipuratum, on this basis, equivalent to one ounce of a potent tincture, would cost about \$2.25, or over twenty-five times as much as the tincture. With digalen the case is even worse. The half ounce containers of this preparation retail on the local market

for the same amount as the digipuratum package, that is, 90 cents. It has been shown, however, that digalen possesses only about one-fourth the physiological activity of the sample tincture. Since digalen retails at \$1.80 an ounce, and since it requires four ounces of digalen to represent one ounce of the tincture, the cost of digalen in an amount equivalent to our four ounce sample would be about \$28 instead of the 40 cents that the latter retails for.

The results obtained with digipoten are given in Table 6.

TABLE 6.—ABSORPTION OF DIGIPOTEN BY CATS

Sex	Weight, Gm.	Mg. Leaf per Kg. Cat	Ether Started, Min.	Emesis, Min.	Died, Min.	Stomach	Oral Dose Absorbed, %
F.	2,180	300	49	0	109	Empty	16.3
F.	2,270	300	30	25	88	Full	12.2
F.	2,146	300	36	49	129	Full	0
F.	1,320	300	18	0	102	Empty	3.4
M.	3,305	300	25	40	65	Empty	13.9
F.	2,000	300	43	25	81	Empty	13.7

As the result of these six experiments, it seems that the absorption of digipoten is slightly more rapid than is the case with the tincture. After an average lapse of 95 minutes, an average absorption of about 13 per cent. of the administered dose occurred. It will be recalled that with the tincture the lapse of time was 112 minutes, with about the same amount of absorption.

When all the facts are taken into consideration, it is apparent that none of the special preparations have advantages over the official tincture from the point of view of absorption which would justify their employment to the exclusion of the former. While digalen is apparently absorbed more readily from the gastro-intestinal tract, the fact that this preparation is of very inferior strength, that different samples show decided variations in strength, and the enormous cost compared with that of a standardized tincture would outweigh the possible advantage of more rapid absorption.

The following conclusions may be drawn:

1. The official tincture of digitalis is absorbed more rapidly from the gastro-intestinal tract of cats than is the infusion made from the same leaf in the manner described.

2. The three special preparations of digitalis, namely, digipuratum, digalen, and digipoten, seem to possess no decided advantage over the official tincture. Digalen is absorbed more rapidly, but the variability in strength and the low standard of strength, together with the high cost of this preparation, more than offset this possible advantage.

VENTRICULAR ESCAPE WITH OBSERVATIONS ON CASES SHOWING A VENTRICULAR RATE GREATER THAN THAT OF THE AURICLES *

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The ventricles occasionally escape from the control of the sinu-auricular node through the independent action of their own center of stimulus production in the atrioventricular junctional tissues. Two types of such ventricular escape should be recognized: first, that which is dependent primarily on a depression of the pacemaker in the sinu-auricular node; and second, that which is dependent primarily on an excitation of the pacemaker in the atrioventricular node. As one would anticipate, examples of the first type are occasionally seen, while instances of the second type appear to be decidedly rare, though both conditions may be more common than we realize at present. The two factors, depression of the sinu-auricular node and the excitation of the atrioventricular node, may be found in a single case. The differentiation between the two types must be based largely on the rate of the sinu-auricular pacemaker from which the ventricles escape and upon the rate of the ventricular pacemaker which escapes. In the electrocardiogram the escaped ventricular complex is normal in shape, similar to that resulting from auricular excitation.

Sometimes the atrioventricular node may manufacture the stimulus for both auricles and ventricles, thus producing true atrioventricular rhythm. This should be distinguished from simple ventricular escape, for in atrioventricular rhythm only one pacemaker controls the heart, while in escape of the ventricles there are two pacemakers, both nodes functioning, the upper node for the auricles and the lower node for the ventricles. Atropin injected subcutaneously may release the lower node from vagal action before it releases the upper node, so that ventricular escape may occur temporarily, as pointed out by Gallavardin, Dufourt and Petzetakis;¹ or true atrioventricular rhythm may occur spontaneously after atropin for a few minutes, as pointed out in one case by Wilson² and as seen in a recent case at the Massachusetts General Hospital (Fig. 1). Wilson has produced this rhythm in a number of

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1. Gallavardin, L.; Dufourt, P., and Petzetakis: *Arch. d. mal du cœur*, 1914, vii, 1.

2. Wilson, F. N.: *THE ARCHIVES INT. MED.*, 1915, xvi, 989.

subjects by the combined effect of early atropin action and ocular pressure or forced respiration. The differential diagnosis between ventricular escape and atrioventricular rhythm is very uncertain without the electrocardiogram. Errors may easily be made in the interpretation of polygrams, in the jugular records of which the *a* and *c* waves almost or completely coincide. Even if the shortened *a-c* or the *c-a* intervals are constant for a considerable stretch of record, ventricular escape may be occurring and not atrioventricular rhythm. In the electrocardiogram, however, we have in the shape of the auricular complex an invaluable clue to the true condition. If the shape of this complex is normal, we have evidence immediately that the sinu-auricular node is

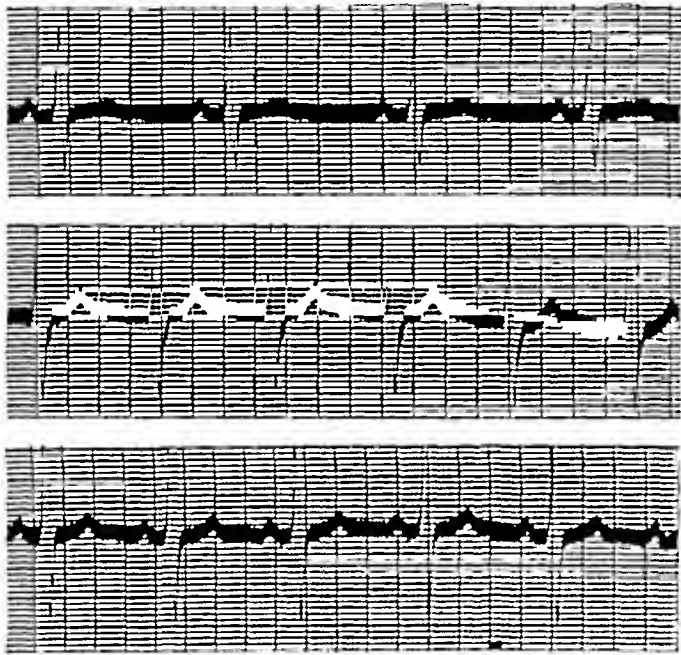


Fig. 1.—Lead 2 of electrocardiogram of E. B. Upper record, before atropin; middle record, fifteen minutes after atropin sulphate 0.002 gm. subcutaneously; and lower record, thirty minutes after the injection of atropin. In the upper and lower records normal rhythm arising in the sinu-auricular node is present; in the middle record occurs a transient atrioventricular rhythm, the inverted auricular complex falling at the end of the first ventricular complex. In all figures abscissae = 0.2 second, ordinates = 10^{-4} volts. The curves in this and the following illustrations are reduced to two-thirds size of the originals.

functioning; if the auricular complex is inverted (in Lead 2), and always at the same time interval immediately before or after the first ventricular complex, we may conclude that the atrioventricular node is probably controlling both auricles and ventricles.

The auriculoventricular dissociation found in ventricular escape is different from that found in complete heart block in that there is usually no defect in auriculoventricular conduction with it. In high-grade heart block, however, ventricular escape may occur as the result

of such a blocking of auricular stimuli that the idioventricular rhythm asserts itself, even though atrioventricular node and bundle may still be able to carry an impulse now and then.

TYPES OF VENTRICULAR ESCAPE

Belonging to the type of ventricular escape for which depression and slowing of the sinu-auricular pacemaker are primarily responsible, are several conditions. When the vagus nerve is overactive, forced expiration may produce a temporary dissociation of the auricles and ventricles, due to marked slowing in the rate of the auricle with resultant escape of the atrioventricular nodal pacemaker, as seen in

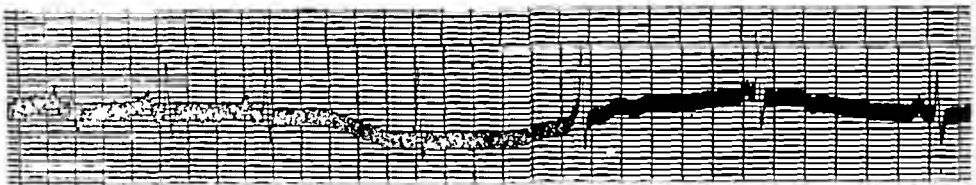


Fig. 2.—Lead 2 of electrocardiogram of G. A. M., showing ventricular escape as the result of forced expiration.

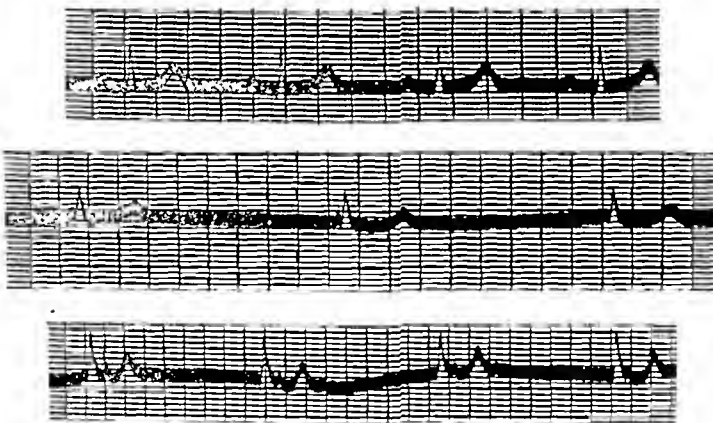


Fig. 3.—Lead 1 of electrocardiogram of G. H. A., showing auriculoventricular dissociation resulting from digitalis. In the upper record occurs the normal rhythm of the patient while not under the influence of digitalis.

Figure 2. Vagal pressure may also act to produce ventricular escape, by depressing the sinu-auricular nodal rate below that of the atrioventricular node (Fig. 6). Digitalis may be responsible for such a situation, as shown by Figure 3. Finally it may occur without obvious cause (Fig. 4). Gallavardin, Dufourt, and Petzetakis¹ have shown that the most varied figures of auriculoventricular superposition in polygrams and electrocardiograms may be produced by intermittent ventricular automatism, as in three patients with bradycardia who came under their observation.

An irritable atrioventricular node may show itself by ventricular escape, even when the rate of stimulus production in the sinu-auricular node is not low. In such cases the ventricular rate may be higher than the auricular rate. Recently at the Massachusetts General Hospital I have seen the ventricular rate spontaneously increased over that of the auricles in a woman 24 years of age who had suffered four weeks before from a peritonsillar abscess and who had had a tonsillectomy under ether four days before the cardiac peculiarity was discovered. She had had no drugs. After her tonsillectomy she had noticed slight but distinct palpitation, which she had never experienced before. Her rate was higher than usual, 90 to 100 instead of about 70. There was occasionally slight quickening of her pulse on palpation; until I obtained graphic records, I thought this slight arrhythmia might be due to auricular premature beats. An electrocardiogram showed auriculoventricular dissociation, with a ventricular rate of 96 and an auricular rate ranging from 67 to 85 (Fig. 5). The interventricular

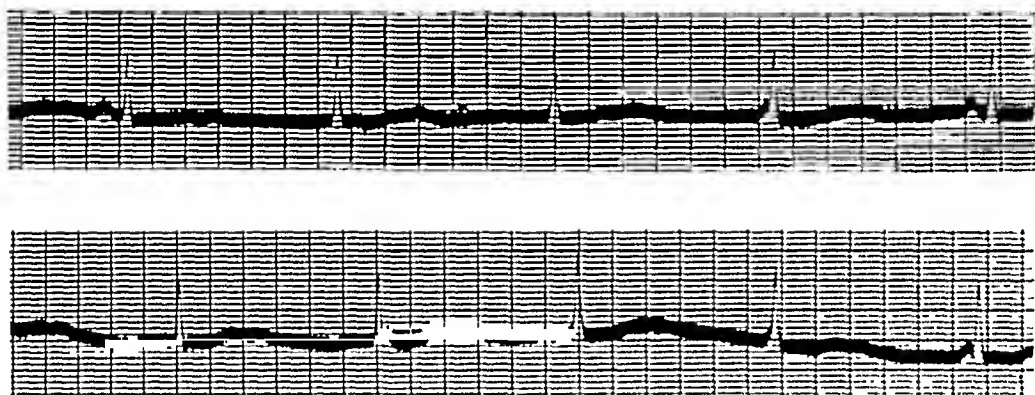


Fig. 4.—Lead 2 of electrocardiogram of A. P., showing auriculoventricular dissociation.

interval of 0.66 second was very constant, except when the auricular excitation came just after the ventricle had recovered from its refractory period and before enough time had elapsed for its escape. At such times the *P* deflection in the electrocardiogram is seen to fall on the *T* wave of the ventricular complex. A shortening of the interventricular interval *R* to *R* results, thus interrupting momentarily the ventricular dominant rhythm in the node of Tawara. In this patient interesting additional evidence was obtained as the result of her resumption of normal rhythm, at a rate of 78 to 83, the day after the dissociation was discovered, and the temporary return of the dissociation as the result of either right or left vagal pressure (Fig. 6). On this day the slowing of the pacemaker in the sinu-auricular node from 80 to 68 allowed the escape of the pacemaker in the atrioventricular node. Here apparently was an irritable atrioventricular node, less irritable on the

second day of examination than on the first, but still irritable enough to escape when the sinu-auricular rate was somewhat slowed. The immediate cause of this irritability appears to have been the tonsillectomy, but the *modus operandi* is a matter of conjecture at present. Aside from the dissociation in this case the heart appeared normal. The patient felt well and was up and about. Wilson³ in 1915 reported a case in which, as the result of forced respiration, a dissociation of auricles and ventricles occurred with a ventricular rate of about 85 and an auricular rate of about 75. This was found in a man of 22 years.

An increase of the rate of the ventricles beyond that of the auricles is uncommon. Lea⁴ in 1915 collected two cases from the literature and reported one himself in which the ventricular rate exceeded that of the auricles in complete heart block. Of these three cases, digitalis

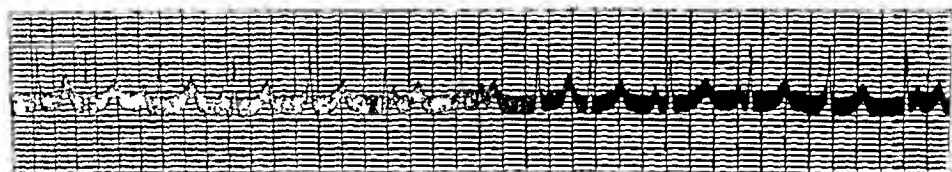


Fig. 5.—Lead 2 of electrocardiogram of J. R. O., showing spontaneous ventricular escape, with higher ventricular than auricular rate.

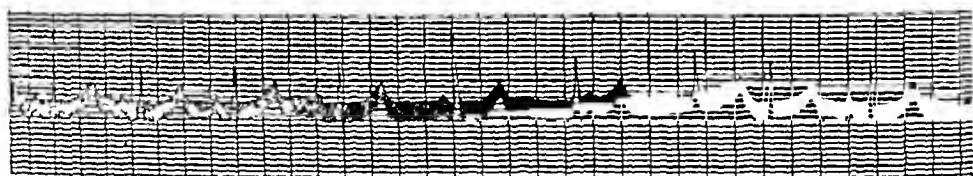


Fig. 6.—Lead 2 of electrocardiogram of J. R. O., showing transient ventricular escape resulting from pressure of left vagus nerve.

was apparently responsible for one (Meyer's) and strophanthus for another (Hewlett and Barringer's); Lea's patient had had no digitalis. A rate of the ventricles higher than that of the auricles occurred temporarily in a case of Gallavardin's¹ and in one of Wilson's² due to ventricular escape resulting from the administration of atropin. Forced respiration resulting in ventricular escape increased the rate of the ventricles over that of the auricles in the case of Wilson,³ to which reference has already been made.

Three cases have come under my observation at the Massachusetts General Hospital which showed increase in the rate of the ventricles over that of the auricles. One, occurring spontaneously, has been described above; the other two can be directly ascribed to digitalis,

3. Wilson, F. N.: THE ARCHIVES INT. MED., 1915, xvi, 86.

4. Lea, Edgar: Lancet, London, 1915, i, 1289.

in one the automatic ventricular rate varying from 65 to 82 while the auricular rate was constant at 41 to 43 (Fig. 7). In the first curve of Figure 7 a regular ventricular action of 82 to the minute occurred, every other beat apparently responding to a regular auricular action of 41 to the minute. In the lower record the shorter interventricular intervals which disturb the dominant rhythm of the ventricles are produced by transient auriculoventricular association, with prolonged *P-R* interval, as the result of the falling of the auricular deflection beyond the refractory period of the ventricle, but not late enough to allow the ventricular pacemaker to escape. In this case both factors in the production of ventricular escape are present. The other case in which digi-

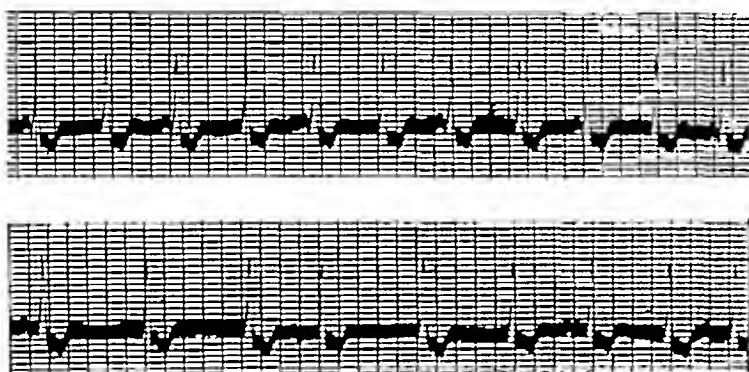


Fig. 7.—Lead 2 of electrocardiogram of E. J. Y., showing ventricular escape resulting from digitalis. In the upper record the ventricular rate is 82 and the auricular rate 41; in the lower record the ventricular rate is 65 and the auricular rate 43.

talis was responsible for the higher ventricular rate, was a patient with atrioventricular rhythm, in whom a curious bigeminy occurred after digitalis. This bigeminy consisted of the sandwiching of an auricular beat between two ventricular contractions; a full description of it may be found in a previous paper by the writer.

SUMMARY

Two types of ventricular escape are described: (1) the occasional type, in which the automatic stimulus production in the atrioventricular node is released by depression, and hence slowing, of the pacemaker in the sinu-auricular node; and (2) the rare type, in which the atrioventricular nodal center of stimulus production is so irritable that it escapes from the control of the sinu-auricular node. Both factors, depression of the upper node and irritation of the lower node, may play a part in ventricular escape in a single case, as in an instance reported, in the production of which digitalis apparently was the important factor. Three cases are recorded in which the ventricular rate exceeded that of the auricles.

A STUDY OF PROTEINS IN URINE

AND A COMPARISON OF GRAVIMETRIC AND NEPHELOMETRIC METHODS
FOR THEIR ESTIMATION *

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AND

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Analytic methods depending on the optical properties of a finely divided suspension have recently achieved considerable prominence. Both the turbidimeter and the nephelometer have been used successfully in quantitative work when the amounts of material were too small to weigh or when the recovery of the substance to be weighed demanded long and tedious manipulation. The quantitative determination of albumin in urine presents many of these difficulties. This fact was pointed out by Folin and Denis¹ in a paper published in 1914, in which a method was described whereby a quantitative estimation of protein in urine could be performed rapidly by means of the turbidimeter. The results obtained agreed well with gravimetric determinations. Since a method depending on the amount of light reflected by a turbid liquid should permit of the determination of smaller quantities of material than one in which the absorbed light is measured, it was thought that the application of the nephelometer to this problem might be of value. While the accuracy of the method proved no greater than that reported by Folin and Denis, some interesting results were obtained and are here presented. Also, since a nephelometer involving slightly new principles had been devised by two of us, it was thought that this problem would afford an opportunity for the systematic comparison of this new instrument with one of the plunger type previously used by Kober and Graves.²

The Marshall and Banks nephelometer used in the preliminary work was built on the frame of a Duboscq colorimeter, but differs in two fundamental respects from the plunger instrument. Instead of a variable length of illuminated column, the suspensions are contained in cells of equal height, somewhat resembling small polariscope tubes. The beam of light is normal to the axes of these cells, as in other nephelometers, and photometric balance is effected by means of a movable wedge of neutral-tinted glass placed above one of the cells. The

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* From the Harriman Research Laboratory, the Roosevelt Hospital, New York.

1. Folin and Denis: *Jour. Biol. Chem.*, 1914, xviii, 273.

2. Kober and Graves: *Jour. Am. Chem. Soc.*, 1914, xxxvi, 1304.

position of the movable wedge is read from a suitable scale with vernier. In making observation photometric balance is first obtained with identical suspensions in both tubes. The wedge reading gives what may be termed the zero point. If now unequal suspensions are compared (the stronger one being placed under the wedge), the illumination of the field will be unequal. By moving the wedge so that the light from the cell below must traverse a greater thickness of absorbing medium, photometric balance is restored. From a calibration of the wedge and the difference between the zero point reading and the new reading, the relative intensities of the lights reflected by the two suspensions may be calculated, as in the case of other wedge photometers. This instrument, therefore, possesses the advantage that the actual ratios of lights reflected from different suspensions may be determined, a very important requirement for the theoretical consideration of the problem of nephelometry in general. The application of this principle to the calculation of results will be referred to later. The determination of the zero reading with each series of observations largely eliminates errors arising from stray light and changes in illumination.

In the first experiments on the estimation of urine protein by means of this instrument the standard (human blood serum) and precipitant (sulphosalicylic acid) recommended by Folin and Denis were used. The results were compared with gravimetric determinations made according to Scherer's method. In determinations on daily specimens of urine from one patient the nephelometric results were consistently about 25 per cent. higher than the gravimetric, while in the case of another individual the nephelometric results showed wide variations from the gravimetric, being usually much higher. This suggested that there was a difference in the nature of the protein excreted by these two individuals. The most probable explanation of such a difference would seem to be that albumin and globulin, while closely related chemically, might give, when precipitated from solutions of equal concentration by sulphosalicylic acid, very different amounts of light, and that in the two cases mentioned the proportion of albumin to globulin was not the same. Since the protein excreted in the urine is at least closely allied to the proteins of the serum, albumin, euglobulin and pseudoglobulin were prepared from horse serum. Solutions of these three proteins were made and standardized by Scherer's method. These solutions were then diluted so that their protein content was the same, precipitated with sulphosalicylic acid and compared in the nephelometer with a standard casein suspension.³

3. This was used as the standard of reference in such comparative work because of the ease with which solutions of known strength may be prepared; furthermore, the precipitation of such solutions with sulphosalicylic acid gives a cloud of great permanence.

It was found that under the above conditions albumin gave about twice as much light as euglobulin and about two and a half times as much light as pseudoglobulin. Mixtures of these protein solutions gave, in general, less light than the constituents singly. It is no doubt safe to assume that the proteins excreted in the urine would behave in a similar manner; and as no definite value for the ratio of albumin to globulin can be assumed in dealing with various specimens of urine, quantitative estimations of total protein should not be made with a precipitant which gives unequal clouds with the different proteins. It is thus evident that sulphosalicylic acid is not satisfactory for the nephelometric determination of protein in urine. Two possible methods of overcoming this difficulty suggested themselves: either to determine the protein fractions separately by accentuating these differences, or to attempt to find a precipitant which would give essentially the same cloud with a definite amount of mixed proteins, no matter how the proportions of albumin and globulin varied. The latter course was decided on. Many of the reagents commonly used for the precipitation of proteins were at once eliminated owing to their evident unfitness for nephelometric work. For instance, any method of precipitation which depends on "salting out" reactions presents many difficulties owing to the high salt content of the solutions used. Again, salts of the heavy metals seem to favor rapid agglutination of the suspension. Trichloroacetic acid fulfilled most of the requirements for a suitable precipitant, but it had to some extent the defect of sulphosalicylic acid; also the amount of cloud varied with the time. Metaphosphoric acid gave practically the same amount of cloud with each of the three protein solutions. A 1 per cent. solution was found to be sufficient for precipitation. An increase in the concentration of the acid up to 5 per cent. had no appreciable effect on the cloud produced. The precipitates, however, agglutinated too rapidly to permit of nephelometric comparison. Of a number of protective colloids tried, gum arabic solution proved the most satisfactory with this reagent and prevented the agglutination of the suspension up to half an hour.

As metaphosphoric acid is never entirely free from the ortho-acid, and as the amount of the latter constantly increases in a solution of the former, it seemed necessary to determine what effect the presence of orthophosphoric acid had on the precipitation.⁴ The following table shows the effect of varying proportions of the two acids in the precipitation of 0.04 per cent. mixed protein solution with gum arabic as a protective colloid.

4. The metaphosphoric acid used was the common glacial stick acid. This contains considerable amounts of ortho-acid and sodium phosphate for which no allowance is made in the above figures. The ortho-acid was syrupy H_2PO_4 , 84 per cent.

TABLE 1.—PLUNGER INSTRUMENT: STANDARD 0.005 PER CENT. CASEIN SOLUTION + SULPHOSALICYLIC ACID; SET AT 20 MM.

Concentration of Acids, per cent.	Meta.	1.0	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0.0
	Ortho.	0.0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
Reading, Min.		23.6	22.7	22.7	22.5	22.7	22.6	22.0	21.9	21.9	22.0	No cloud

With the mixture 0.4 per cent. metaphosphoric acid and 0.6 per cent. ortho-acid the slight decrease in the reading indicates a slight increase in the cloud. An increase in the proportion of the ortho-acid produces no further change up to and including the ratio of 1 to 9. Thus the precipitation appears to be more complete with a solution containing an excess of orthophosphoric acid. As the amount of this acid has no effect between the limits indicated, it was decided to use as the precipitant a mixture containing 0.6 per cent. and 0.4 per cent. of the ortho-acid and meta-acid respectively. A large amount of the meta-acid may thus be hydrated before a noticeable change occurs in the cloud.⁵

TABLE 2.—PLUNGER INSTRUMENT: STANDARD 0.005 PER CENT. CASEIN + SULPHOSALICYLIC ACID; SET AT 20 MM.

Relative Amounts of 0.04 per Cent. Protein Solution			Readings, Min.		
Albumin	Euglobulin	Pseudo- globulin	5 Min.	10 Min.	15 Min.
10	0	0	21.7	21.6	21.5
0	10	0	21	20.9	21.1
0	0	10	21.5	21.5	21.5
6	2	2	21.5	21.5	21.6
8	1	1	21.6	21.5	21.6
5	2.5	2.5	21.2	21	21.1
4	3	3	21	21.2	20.9

It was then necessary to determine what variations there were in the clouds produced when the three proteins separately and mixed were precipitated by this reagent in the presence of gum arabic. The comparisons were made as before against a standard casein solution precipitated by sulphosalicylic acid. Five c.c. of 0.04 per cent. protein

5. Experiments in duplicating the hydrogen ion concentration of this mixture by adding hydrochloric acid to solutions of metaphosphoric were inconclusive, due possibly to the difficulty of employing indicators with phosphoric acids. Thus we cannot at present say whether the change in hydrogen ion concentration is alone responsible for the effect. At all events, the mixture of the two phosphoric acids appeared to be the most satisfactory reagent.

solution were used in each case; to this were added 5 c.c. of 1 per cent. gum arabic solution, and, after thorough mixing, 20 c.c. of the reagent run in from a pipette. Readings were made at intervals of five, ten and fifteen minutes after precipitation. Agglutination did not occur for more than thirty minutes.

From these results it is evident that there are no appreciable differences between the proteins themselves or various mixtures of them as regards the clouds produced under these conditions.

The next consideration was to determine upon a satisfactory standard. Nephelometric results may be interpreted quantitatively in one of two ways: either the substance to be determined may be compared to a solution of known strength of the same substance, or it may be compared to a purely arbitrary standard. In the present problem the former of these methods was not entirely practicable, owing to the difficulty of preparing pure urine proteins. Again, in dealing with these proteins the solutions cannot be made up to a given strength by weighing out the dried substance and dissolving in a known volume of water; the solution must be standardized by some other method. Since, then, the identical substance cannot be used as a standard, an attempt was made to realize the conditions of the first method as closely as possible. The assumption was made that since the various serum proteins showed no differences with this precipitant, the closely related urine proteins should give the same amount of cloud. Thus, if two solutions, one of urine protein, the other of serum protein, give in the instrument identical clouds, we may assume that they contain equal amounts of protein. An aqueous solution of serum proteins may be standardized with reasonable accuracy by nitrogen estimation⁶ or by gravimetric determination of the heat coagulable protein. In the case of protein in urine such a standardization obviously presents many difficulties, owing to adsorption of other ordinary constituents. Serum protein, however, is not a convenient standard for practical work, for when the serum is not perfectly fresh, the suspensions agglutinate rapidly.

Other proteins were then investigated. It was found that solutions made from commercial dried egg-albumin and standardized gravimetrically gave the same cloud in the instrument as serum protein solutions of the same strength similarly standardized. It is thus evident that such a solution may be substituted for the serum protein solution as a standard. This is desirable in that egg-albumin is easily obtained and solutions are readily prepared and standardized. The standard solution of this substance was prepared as follows: About 5 gm. of

6. Allowance for nonprotein nitrogen must be made and in the gravimetric determinations precautions described later must be observed.

commercial dried egg-albumin were dissolved in 450 c.c. of water, with the addition of 2 gm. of powdered talc. After agitation 50 c.c. of 2 per cent. tricresol were then added and the mixture filtered through a fluted paper. This gave a nearly clear solution containing about 9 mg. of heat-coagulable protein per cubic centimeter. Furthermore, egg-albumin solutions prepared as described above are very stable and thus large quantities may be made up at one time. For example, a solution containing at the time of preparation 9.2 mg. of coagulable protein per cubic centimeter contained after forty days 9 mg. per cubic centimeter.

TABLE 3

Protein	Amount and Dilution, C.c.	Mg. Protein Recovered	Mg. Nitrogen in Protein	Per Cent. Nitrogen in Protein	Mg. Nitrogen in Filtrate
Egg-Albumin, Solution 1, 10 c.c. = 7.89 Mg. N.	5 + 95 water.....	23.5	3.52	14.98	0.54
	10 + 90 water.....	46.3	7.02	15.17	1.05
	20 + 80 water.....	92.1	13.88	15.08	1.95
Egg-Albumin, Solution 2, 10 c.c. = 15.96 Mg. N.	10 + 490 water.....	91.9	13.63	14.84	1.90
	10 + 150 water.....	92.4	13.94	15.10	1.84
	10 + 120 water + 20 normal urine	90.5	13.84	15.28
	10 + 100 water + 40 normal urine	92.4	13.95	15.11
	10 + 90 water boiled 1 hour.....	93.0	14.04	15.10	1.75
	10 + 90 water excess acetic acid	92.8	14.11	15.20	1.85
Serum-Albumin Solution, 10 c.c. = 12.36 Mg. N.	5 + 95 water.....	79.3	11.74	14.80
	10 + 90 water.....	158.8	23.26	14.80	1.25
	20 + 80 water.....	319.5	46.30	14.79	2.60
	5 + 95 normal urine.....	79.4
	10 + 90 normal urine.....	157.4

As previous work had given evidence that it was difficult to obtain reproducible results by Scherer's gravimetric method, a study of some of the factors involved in the coagulation, filtration and drying of egg-albumin, serum protein and urine protein was undertaken. This was necessary, as a consistent standard of comparison was essential to the interpretation of the nephelometric results. Solutions of the proteins mentioned were coagulated by heat with the cautious addition of 1 per cent. acetic acid. The coagulated protein was then filtered on weighed Gooch crucibles,⁷ washed with hot water, finally with alcohol, and dried

7. These were used to eliminate the uncertainties arising from the use of the weighed filter papers usually recommended.

at from 100 to 105 C. to constant weight. In a number of cases drying was found to require as much as two days; after this there was no further loss of weight. The crucibles were cooled over phosphorus pentoxid for one hour before weighing. The filtrates, although clear, were always tested with sulphosalicylic acid for uncoagulated protein.

Aqueous solutions of egg-albumin were first studied. The total nitrogen content of the solution was determined by the Kjeldahl method; portions were then coagulated and filtered as described above. Kjeldahl determinations were also made on the filtrates and on the coagulated protein in the crucibles.⁸ The nitrogen determinations on the coagulated protein agreed with the figures recorded by other investigators only when the foregoing precautions in drying were observed.

Changes in the dilution, in the amount of protein present, in the amount of acid, and in the time of heating were studied. In some cases normal urine was added as shown in Table 3, where the results are recorded.

The results show that when the precipitates are dried to constant weight, the conditions of precipitation may vary considerably and still permit of reproducible results in the amount of protein recovered. Even in the presence of normal urine there is apparently no error due to adsorption.⁹

The nitrogen content of the coagula agrees well with the figure found (15.21 per cent.) for larger quantities of egg-albumin coagulated and dried to constant weight, and is in good agreement with the accepted value. The sum of the protein nitrogen and the nitrogen of the filtrate approximates very closely the nitrogen of the solution. As is shown (column 5, Table 3), the nitrogen of the filtrates is directly proportional to the amount of protein coagulated. Nonprotein nitrogen determined by the Greenwald method¹⁰ gave about 0.1 mg. in 10 c.c. of solution. Further experiments showed that the high nitrogen of the filtrates from the coagula was due to ovomucoid contained in egg-albumin. This substance is not precipitated by trichloracetic acid, but is removed by the kaolin used in the Greenwald method.

The coagulation of the protein in pathologic urine was then studied in the same manner, except that for obvious reasons the nitrogen of the filtrate was not determined. By following the method here outlined the results checked very closely where duplicate determinations

8. Any protein which adhered to the beaker was digested in the beaker with 1 c.c. sulphuric acid and the nitrogen determined. The amounts found were in most cases negligible.

9. The high color of protein coagulated from pathologic specimens containing albumin would, however, indicate considerable adsorption.

10. Greenwald: Estimation of Nonprotein Nitrogen in Blood, *Jour. Biol. Chem.*, 1915, xxi, 61.

were made, and the errors due to solution, adsorption, etc., were at least constant for a given specimen of urine, although it is highly probable that the absolute amount of protein present was not obtained. The nitrogen in the coagulated urine protein was always lower than expected.

The study of the nephelometric determination was then undertaken. Since the light observed in the instrument is not proportional to the amount of material, the relationship between concentration and instrumental readings must be determined for the substance and the precipitant. This may be done by observing in the instrument suspensions prepared from solutions of known relative concentrations, irrespective of their absolute concentrations.¹¹ The solutions for comparison were prepared as follows: A urine containing albumin was suitably diluted for use as a stock solution. A series of solutions was then prepared from this by taking quantities of 9 c.c., 8 c.c., 7 c.c., 6 c.c. and 5 c.c. and making each up to a volume of 10 c.c. with distilled water. These were then precipitated and compared in the instruments with the stock solution similarly precipitated. From the readings thus obtained a curve was drawn by plotting the ratio of concentration against the readings of the instruments. These curves may now be used in the determination of protein solutions of unknown concentration, by means of a suitable standard. Either the ratio may be read directly from the curve, or it may be calculated from the equation of the curve. The latter method was used throughout this investigation. In the plunger instrument the following formula¹² was used:

$$y = \frac{s}{x} - \left[\frac{1-x}{x^2} \right] sk$$

The value of k in this case was found to be 0.20. In the wedge instrument the somewhat similar curve is also capable of formulative interpretation. It was found that by plotting the wedge readings less the zero point reading against the logarithm of the ratio, a straight line resulted. The ratio may thus be expressed by the following formula:

$$\left[\log. \frac{1}{R} = KW' \right]$$

In this formula W' is the wedge reading less the zero reading, R is the ratio of the weaker solution to the stronger; K , a constant depending on the substance and the precipitant used, is determined from the

11. A precaution to be exercised is that the solutions must not be too dilute to be read conveniently, or so strong that they agglutinate rapidly.

12. Jour Biol. Chem., 1913, xiii, 491.

observations on known ratios referred to above.¹³ The evaluation of K from known ratios of urine protein is given in Table 4. When the ratio to the standard has been obtained, the calculation of the amount of protein simply depends on the protein content of the standard and the dilution of the unknown urine. It is advisable to dilute the urine so that the ratio to the standard is fairly close to unity.

TABLE 4.—EVALUATION OF CONSTANT K *

W	7.8	16.0	26.6	41.0	54.4
R	0.9	0.8	0.7	0.6	0.5
$K \times 10^3$	5.9	6.0	5.8	5.4	5.5

* The weighted mean, $K = 5.7 \times 10^3$, was used.

The method of precipitation used throughout this investigation was as follows: Five cubic centimeters of standard egg-albumin solution containing about 0.5 mg. protein per cubic centimeter and 5 c.c. of previously diluted urine were measured into dry Erlenmeyer flasks. To each flask was then added 5 c.c. of 1 per cent. gum arabic solution, and finally 20 c.c. of the phosphoric acid reagent. The suspensions were then compared in the nephelometer and the calculations performed as has been indicated. The gum arabic solution should be prepared fresh each day, but this presents little difficulty, as extreme accuracy is not necessary. The stability of the standard has already been referred to. The precipitant (0.6 per cent. orthophosphoric, 0.4 per cent. metaphosphoric) was prepared each day from 5 per cent. solutions of the two acids. It was found that the 5 per cent. solution of metaphosphoric acid after standing ten days was still satisfactory for the preparation of the reagent, for even though much of the acid may have been hydrated in this time, if the proportion of orthophosphoric did not exceed 90 per cent. of the total acid, the precipitating power of the mixture apparently was not altered.

In the case of urines highly colored with bile pigments, blood, etc., color may interfere with the determination. With such specimens the difficulty may be overcome by the following procedure: Two equal portions of the urine are taken, to one of which is added a known amount of the standard egg-albumin solution, and each then made up to an equal volume with water and compared in the usual manner. The original protein content of the urine may thus be obtained indirectly,

13. Since the light is an exponential function of W it can easily be shown that the light reflected by a suspension is equal to $C^{K/k}$ where C is the concentration of the suspension and k is a constant depending on the particular wedge used. K has been referred to previously.

and difficulties arising from differences of color are entirely obviated. It was not necessary to use this method in any of the determinations listed below, but experience has shown that it is eminently practicable, though somewhat less accurate than the direct method.

Nephelometric determinations were made on daily specimens of urine from several nephritics during a period of several weeks. The protein content of each specimen was also determined gravimetrically in the following manner: The protein was coagulated by heat and dilute acetic acid, filtered on weighed Gooch crucibles, washed with hot water and alcohol and dried in the air oven at 100 to 105 C. for two days. The filtrates were tested with sulphosalicylic acid for uncoagulated protein. The nitrogen content of the protein recovered was in each case determined by the Kjeldahl method.

Although the inaccuracies of the Esbach determination are well known, it is so much used in clinical practice that it was thought advisable to make such determinations on a number of specimens in this series. These determinations were made in the usual manner and were read after standing twenty-four hours. All these results are included in Table 5, which presents a summary of work on urine.

It may also be seen from column 1 (Table 5) that the actual amount of protein recovered was seldom less than 60 mg. We have found that satisfactory duplicate determinations can readily be made on amounts of protein of about this order. Column 2, the percentage of nitrogen in the protein recovered, is remarkably consistent in the cases of W. and M. In the other two cases studied we find decidedly greater variations. The average of W. and M. (14.3 per cent.) is much lower than would be expected for protein of this kind. The factor, 6.3, recommended in the literature for calculation of urine protein content from the nitrogen content of the coagulum, corresponds to a nitrogen percentage of 15.88. This is very much above the average nitrogen value even in cases Mc. and C. (14.6 per cent. and 15 per cent., respectively). This would indicate that occlusion of substances low in nitrogen was considerable and that the weight of the dry coagulum was not the weight of protein present in the sample of urine taken for analysis. This may be partially compensated for by the fact that it is not possible to obtain absolutely complete coagulation of the protein. The filtrates, however, never showed more than a slight trace of protein on the addition of sulphosalicylic acid and were generally protein free by this test. The error from this cause is therefore small. Columns 3, 4 and 5 are self-explanatory.

Columns 6 and 7 give the ratio of the determinations by the two nephelometers to those by the gravimetric method. In the case of W. the nephelometric determinations are, on the average, lower than the gravimetric. With M. the difference is less, but still in the same sense

TABLE 5.—PROTEIN DETERMINATION OBTAINED BY VARIOUS METHODS

Sub- ject	Date	1 Gravi- metric, Mg. Weighed	2 Kjel- dahl, per Cent. N	3 Gravi- metric, Mg. per G.e.	4 Plunger Neph., Mg. per G.e.	5 Wedge Neph., Mg. per G.e.	6 Col. 4 Col. 3	7 Col. 5 Col. 3	8 Esbaeh, Mg. per G.e.
W.	Feb. 2	157.3	15.7	13.9	14.9	0.884	0.947
	3	164.9	14.53	16.5	13.0	15.6	0.788	0.946
	4	195.2	14.24	19.5	18.4	17.7	0.943	0.907
	5	72.9	14.32	14.6	13.9	0.953
	14	66.0	14.27	13.2	11.6	0.878	11.6
	17	76.1	15.2	13.0	14.0	0.854	0.923	10.8
	18	54.0	14.26	10.8	10.2	0.944
	20	59.0	14.10	11.8	11.5	11.5	0.975	0.978	5.8
	24	179.1	14.24	17.9	19.0	1.061	8.6
	25	80.2	14.69	16.0	14.6	16.5	0.910	1.028	12.0
	26	93.9	14.35	18.8	17.5	18.7	0.932	0.996	12.4
Average.....			14.34	0.901	0.971	
Probable error {Mean..... Single deter- mination...			±0.03	±0.013	±0.011	
			±0.11	±0.038	±0.033	
M.	Feb. 4	32.6	14.42	3.26	3.04	0.932
	5	76.4	3.06	3.00	2.99	0.982	0.978
	15	102.6	14.29	2.05	2.05	1.001	1.3
	16	84.5	14.38	3.38	3.12	0.932	2.3
	17	71.7	14.61	2.86	2.68	2.94	0.927	1.025	1.8
	18	69.6	14.18	2.78	2.69	0.967
	19	76.6	3.06	2.95	3.02	0.963	0.987	1.7
	20	62.2	14.29	2.49	2.51	2.51	1.009	1.009	1.4
	24	129.8	13.84	5.19	4.97	5.38	0.957	1.036	2.7
	25	130.7	14.38	5.23	5.24	1.002	4.3
	26	96.3	14.63	3.85	4.06	3.75	1.054	0.973	3.6
Average.....			14.30	0.978	0.991	
Probable error {Mean..... Single deter- mination...			±0.05	±0.018	±0.008	
			±0.15	±0.057	±0.021	
Me.	Feb. 18	38.4	1.54	1.94	1.262
	20	54.3	13.87	1.09	1.27	1.25	1.170	1.152	0.5
	23	36.1	0.72	0.94	1.00	1.303	1.365
	24	28.9	14.78	0.58	0.90	0.91	1.537	1.583	0.5
	25	66.7	15.14	1.33	1.64	1.62	1.229	1.213	1.2
	26	83.6	14.56	3.34	3.50	3.94	1.047	1.178	3.3
Average.....			14.60	1.261	1.302	
Probable error {Mean..... Single deter- mination...			±0.14	±0.047	±0.055	
			±0.31	±0.115	±0.123	
C.	Feb. 2	99.4	14.38	3.08	4.17	3.87	1.048	0.973
	3	82.8	15.06	3.31	3.75	3.33	1.132	1.006
	4	102.9	15.75	4.12	4.17	1.012
	5	90.1	14.62	3.60	3.66	3.57	0.991	0.991
Average.....			14.98	1.060	0.995	
Probable error {Mean..... Single deter- mination...			±0.20	±0.026	±0.006	
			±0.40	±0.045	±0.012	

With Mc., however, the average is nearly 30 per cent. higher than the gravimetric determination. Again, with C. the ratio is very nearly unity. As for the explanation of these irregularities, it may be said in the first place that the gravimetric determination cannot be taken as the value of the absolute amount of protein present. Calculation of the results on the basis of the nitrogen content of the coagulated protein did not improve agreement—in fact the probable error of these determinations was greater than when the nephelometric determinations were referred to the gravimetric. This would indicate that while there may be errors in the gravimetric method, due to occlusion and other causes, the main source of the error lies in the nephelometric determinations themselves. These irregularities are probably due to differences in the form of the precipitants under different conditions. As the urines must be diluted according to their protein content, the amounts of the other urinary constituents will vary considerably. The effect of varying salt concentration on the state of a finely divided suspension is well known. The very large variations in the case of Mc. can hardly be accounted for in this way. The nitrogen value of the coagulated protein was not constant in successive specimens. The presence of a variable amount of mucoid might have some influence on the precipitation of albumin in the nephelometer. This is not precipitated by an excess of metaphosphoric acid, but it may act as a protective colloid and thus influence the state of protein precipitation. Removal of patient Mc from the hospital prevented a further study of this interesting irregularity.

From column 8 it may be seen that the Esbach determination did not agree with the nephelometric or the gravimetric, in the majority of cases being from 25 to 50 per cent. lower.

The probable errors show slightly more consistent results with the wedge instrument.

We may safely conclude that the nephelometric method is satisfactory for clinical purposes; and that the results are in fair agreement with those obtained by the gravimetric method. For urines of low protein concentration the method is no doubt more accurate than the gravimetric. It is much more rapid than the gravimetric or the Esbach determinations.

SUMMARY

1. A nephelometric method, using egg-albumin as a standard, for the determination of protein in urine has been described.

2. A new type of instrument has been used and a formulative expression for the relation between light and concentration has been given.

3. The factors involved in the quantitative recovery of protein from urine have been studied.

4. The nitrogen content of the protein recovered has been found to be lower than the generally accepted values in the case of urine protein.

5. Results with the wedge and with the plunger instruments have been compared with a gravimetric method.

The authors wish to express their thanks to Mr. Herbert Eckweiler for his careful work in the nitrogen determinations.

TRANSIENT AURICULAR FIBRILLATION

AN ELECTROCARDIOGRAPHIC STUDY *

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In this communication are presented the results of a detailed study, by means of the electrocardiograph, of six individuals exhibiting the change from a normal heart rhythm to that of auricular fibrillation. Although the disturbance of cardiac mechanism that causes this type of cardiac irregularity—incoordinate contraction or fibrillation of the auricular musculature—has been understood only during the past few years, its clinical prototype, the *pulsus irregularis perpetuus* of Hering, or the totally irregular pulse, has for years been recognized as one of the commonest as well as one of the gravest forms of cardiac arrhythmia. Perhaps from the widespread use of Hering's terminology, however, the erroneous impression has been prevalent that this condition once present is practically always permanent. Already a sufficient number of cases have been published to combat this view, so that we must now consider that auricular fibrillation, like the other disturbances of the cardiac mechanism—premature contractions, heart block and alternation—may, though less frequently, occur in a transitory as well as a permanent form. My main thesis will be to show not only that transient auricular fibrillation constitutes a well recognized condition, but that it may be subdivided into three well-defined groups.

REVIEW OF THE LITERATURE

Cushny and Edmunds,¹ in the paper that first propounded the theory that a totally irregular pulse is due to fibrillation of the auricles, were led to their experimental work by the study of a woman who had had numerous paroxysmal attacks of fibrillation during several years of observation. No determining factor was discovered clinically, but the conclusion was reached that the attacks were due to reflex vagus inhibition.

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* From the John Herr Musser Department of Research Medicine, University of Pennsylvania, Philadelphia.

1. Cushny, A. R., and Edmunds, C. W.: Paroxysmal Irregularity of the Heart and Auricular Fibrillation. *Am. Jour. Med. Sc.*, 1907, cxxxiii, 66.

Very similar cases have been reported by Fox,² Hornung,³ G. C. Robinson,⁴ Popper,⁵ and Lewis and Schleiter.⁶ These patients, as was Cushny and Edmund's patient, were all over 50 years of age and had had numerous attacks, lasting from a few minutes or hours to several days, and extending over many years. In none was a valvular defect present, but hypertension and preponderance of the left ventricles were found in all. Another interesting group of ten cases has been reported by Heitz,⁷ together with polygraphic records, which unfortunately do not absolutely preclude the existence of some other form of arrhythmia. In another series, out of a total of 120 patients with auricular fibrillation examined electrocardiographically, Fahrenkamp⁸ found only four in whom the trouble was transient (3.3 per cent.). Though paroxysmal in character, the attacks were all single and short (one fatal), seen in acute conditions, such as Graves' disease, pneumonia and septicemia. Further details of these cases will be considered later, in connection with the discussion of the cases here reported. The cases reported by Falconer and Dean⁹ and by Schwarzmänn¹⁰ developed transient attacks of fibrillation in the presence of an already existing heart block. The complication that this causes makes it inadvisable to include them in this discussion.

The older theory that a temporarily but totally irregular pulse (delirium cordis) is not uncommon and frequently disappears under digitalis medication was in most cases due to imperfect observation. The probability is that in such cases the slight degree of arrhythmia, which became still less with the improvement of the patient, became unnoticeable to the touch, in spite of the fact that the underlying condition of fibrillation persisted. In some cases, also, as Fahrenkamp and others have pointed out, the occurrence of complicated groups of extrasystoles may (in the absence of electrocardiograms) present a picture indistinguishable from auricular fibrillation.

2. Fox, G. H.: Transitory Delirium Cordis, *Am. Jour. Med. Sc.*, 1910, cxl, 815.

3. Hornung, O.: Ueber atypische tachykardische Paroxysmen, *Deutsch. Arch. f. klin. Med.*, 1907, ??, 469.

4. Robinson, G. C.: Paroxysmal Auricular Fibrillation, *THE ARCHIVES INT. MED.*, 1914, xiii, 298.

5. Popper, H.: Ueber Anfälle von Vorhofflimmern, *Med. Klin.*, 1915, xi, 885.

6. Lewis, T., and Schleiter, H. G.: The Relation of Regular Tachycardias of Auricular Origin to Auricular Fibrillation, *Heart*, 1911-1912, iii, 173.

7. Heitz, J.: La forme paroxystique de l'arythmie complete, *Ann. de méd.*, 1914, i, 483.

8. Fahrenkamp, K.: Vorübergehende komplette Herzunregelmässigkeiten unter dem klinischen Bilde der Ahythmia Perpetua mit Beobachtungen über Vaguswirkung, *Deutsch. Arch. f. klin. Med.*, 1914, cxvii, 1.

9. Falconer, A. W., and Dean, G.: Observations on a Case of Heart Block Associated with Intermittent Attacks of Auricular Fibrillation, *Heart*, 1911-1912, iii, 247.

10. Schwarzmänn, G. S.: Ueber ein Fall von Herz Block mit Paroxysmalem Vorhofflimmern, *Zentralbl. f. inn. Med.*, 1914, xxxv, 1001.

The six cases of fibrillation mentioned above are here reported in detail, in the hope that they may throw some light on the poorly understood pathogenesis of this common and serious condition and on the prognosis of such transient cases. The fibrillation in four of the cases was found to be transient, and in the other two cases developed while the patients were under observation. These four represent 7.5 per cent. of the total number of cases of auricular fibrillation studied electrocardiographically at the University Hospital during a period of two

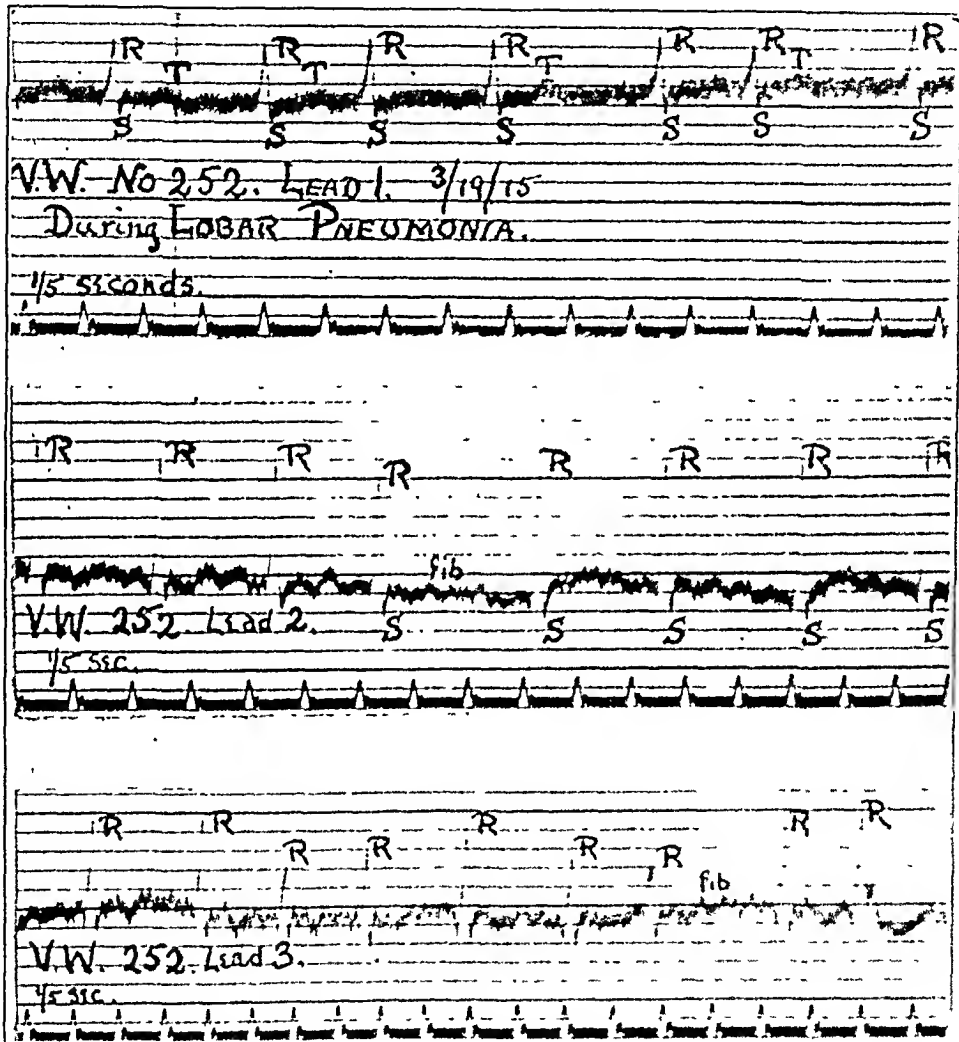


Fig. 1 (Case 1).—Electrocardiogram of V. W., showing transient auricular fibrillation in lobar pneumonia. In this, as in other electrocardiograms of this series, records were taken from the three customary leads. The tension of the string was so standardized that 1 millivolt caused a deflection of 1 cm. As the string could not be standardized with the patient in circuit, 1,400 ohms were added as an arbitrary equivalent of the patient's resistance. Platinum string, resistance about 3,500 ohms. Time intervals are expressed in fifths of second and occasionally by vertical lines indicating $\frac{1}{5}$ and $\frac{1}{10}$ second. In this figure, note (1) absence of sign of auricular contraction (P wave); (2) ventricular arrhythmia (irregular occurrence of R); and (3) occasional coarse waves of fibrillation.

and a half years. While this is apparently an unusually high percentage of transient fibrillation, it is very probable that the wider use of graphic methods of registration will in the near future demonstrate its greater frequency.

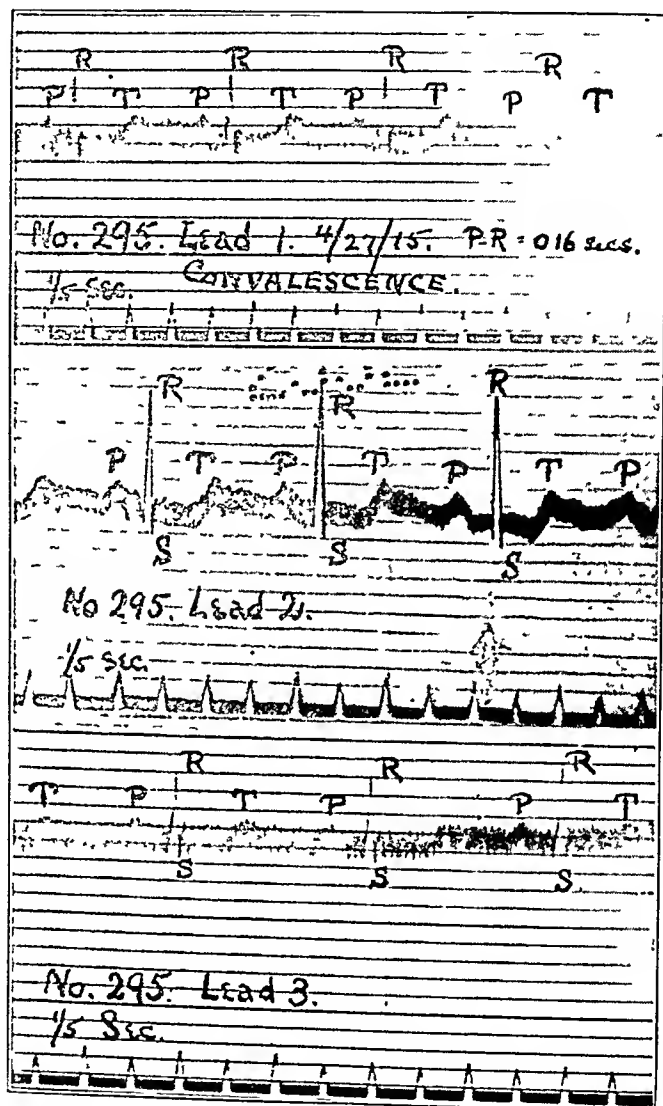


Fig. 2 (Case 1).—Electrocardiogram of same patient as in Figure 1, showing normal rhythm during convalescence from pneumonia. Note reappearance of P wave, regular occurrence of R and absence of fibrillation waves. (The print of Lead II, as in a few other instances, has been retouched for purposes of reproduction.)

I. TRANSIENT AURICULAR FIBRILLATION IN LOBAR PNEUMONIA

CASE 1.—V. M., a white man, married, 53 years old, a tinsmith by trade, was admitted to the hospital March 17, 1915, on the third day of a typical attack of lobar pneumonia, involving the left lower lobe. A total arrhythmia was noticed on admission, although the patient had never noticed such arrhythmia before and had never to his knowledge had any previous cardiac trouble. Cardiac dulness was not increased and there were no valvular murmurs. Except

for two attacks of gonorrhea twenty-five years before, he had never been seriously ill. He had never had rheumatism, tonsillitis or other fever, although a later blood examination gave a positive Wassermann reaction. The systolic blood pressure on admission was 120, diastolic 95. After the reestablishment of normal rhythm, the systolic pressure was 115, diastolic 85.

An electrocardiogram (Fig. 1) taken on the day of admission showed the presence of auricular fibrillation (of the coarse type), absence of the P wave and a moderate degree of arrhythmia. The form of the electrocardiogram shows no other deviation from the normal, except that the T wave is inverted in Lead III. Tincture of digitalis (0.6 c.c. three times a day) was begun at once and continued during the patient's stay in the hospital of more than a month. Although the pneumonic crisis was reached in four days after admission, with normal resolution of the involved lobe, the pulse rate remained over 100 for another ten days. The arrhythmia became less and less marked, until one month after admission, with the pulse rate varying between 60 and 90, arrhythmia was imperceptible. An electrocardiogram (Fig. 2) taken at this time showed a regular rhythm, with the reappearance of the P wave. The T wave in Lead III is no longer inverted and is more pronounced in the other two leads than in the former record. The patient was discharged in good condition and since then has had no return of any cardiac irregularity. A polygram (Fig. 3) taken three months later revealed a regular radial pulse (rate 62 beats per minute) with a normal jugular pulse. The fact that the myocardium had not yet returned to normal, however, was shown by the persistence of pretibial edema and dyspnea on exertion.

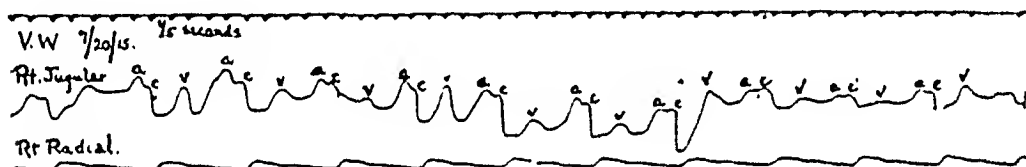


Fig. 3 (Case 1).—Normal polygram three months after pneumonia. Note regular radial rhythm and normal "a, c, v" type of venous pulse, with prominent "a" wave.

Summary of Case.—A patient in the third day of an attack of lobar pneumonia was found to have auricular fibrillation with considerable arrhythmia, although there had been no previous history of heart disease. After recovery from the pneumonia, the arrhythmia gradually decreased, until one month later the electrocardiogram showed a normal P wave and regular rhythm. The exact time at which the auricle began again to beat coordinately was not determined, but was apparently not accompanied by any noticeable subjective symptoms or change in rate. That the return to a normal rhythm was permanent is shown by polygraphic records taken three months later.

II. TRANSIENT AURICULAR FIBRILLATION OF NERVOUS ORIGIN IN SYPHILITIC MYOCARDITIS

CASE 2.—B. A., a white woman, married, 38 years old, was admitted to the hospital March 2, 1915, for the removal of a uterine fibroid. She had had measles, mumps, appendicitis and typhoid, but had totally recovered from each, and had otherwise been healthy. Her husband was living and well, but she had had no children, one miscarriage, and the Wassermann reaction was strongly positive. She had never complained of any cardiac trouble until three

weeks before admission, at which time after a hard day's work she had an attack of palpitation, dyspnea and irregular heart action. Another attack occurred the next evening and the symptoms continued more or less marked until admission to the hospital. On the day of admission she had a similar

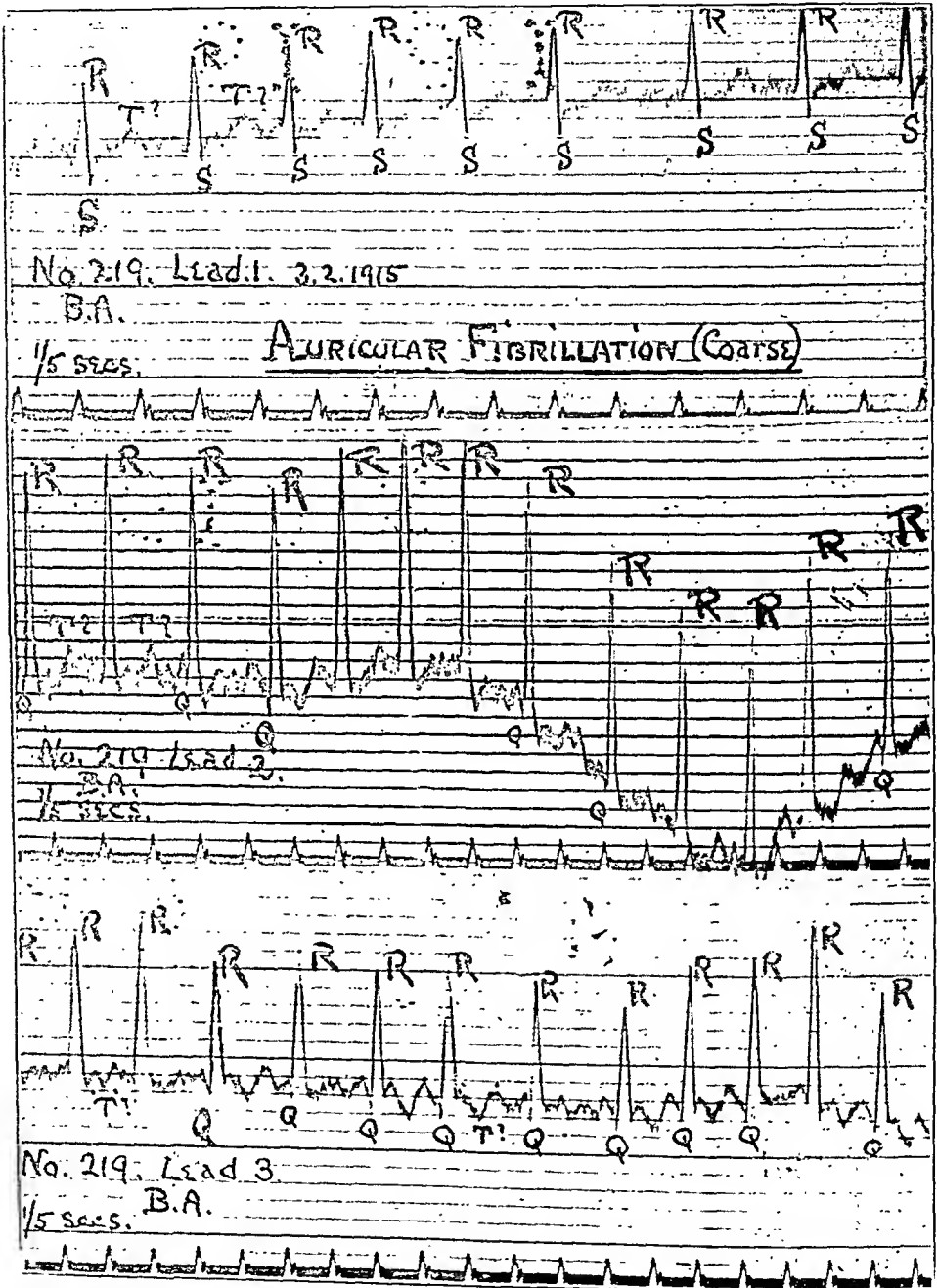


Fig. 4 (Case 2).—Electrocardiogram of Mrs. B. A., taken March 2, 1915, showing transient auricular fibrillation in syphilitic myocarditis. Note same disturbances of mechanism as in Figure 1.

attack, but more serious than any previous one, and the extreme rapidity and irregularity of the heart action necessitated the abandonment of the operation. The patient attributed this attack to the nervous excitement aroused by contemplation of the operation.

At the time of the electrocardiographic study she was in a very nervous state, with warm, flushed skin, and marked tremor of the hands. The radial pulse was distinctly irregular, rapid (180 per minute), quick, full, with increased tension, the wall slightly sclerotic. The cardiac dulness was slightly increased

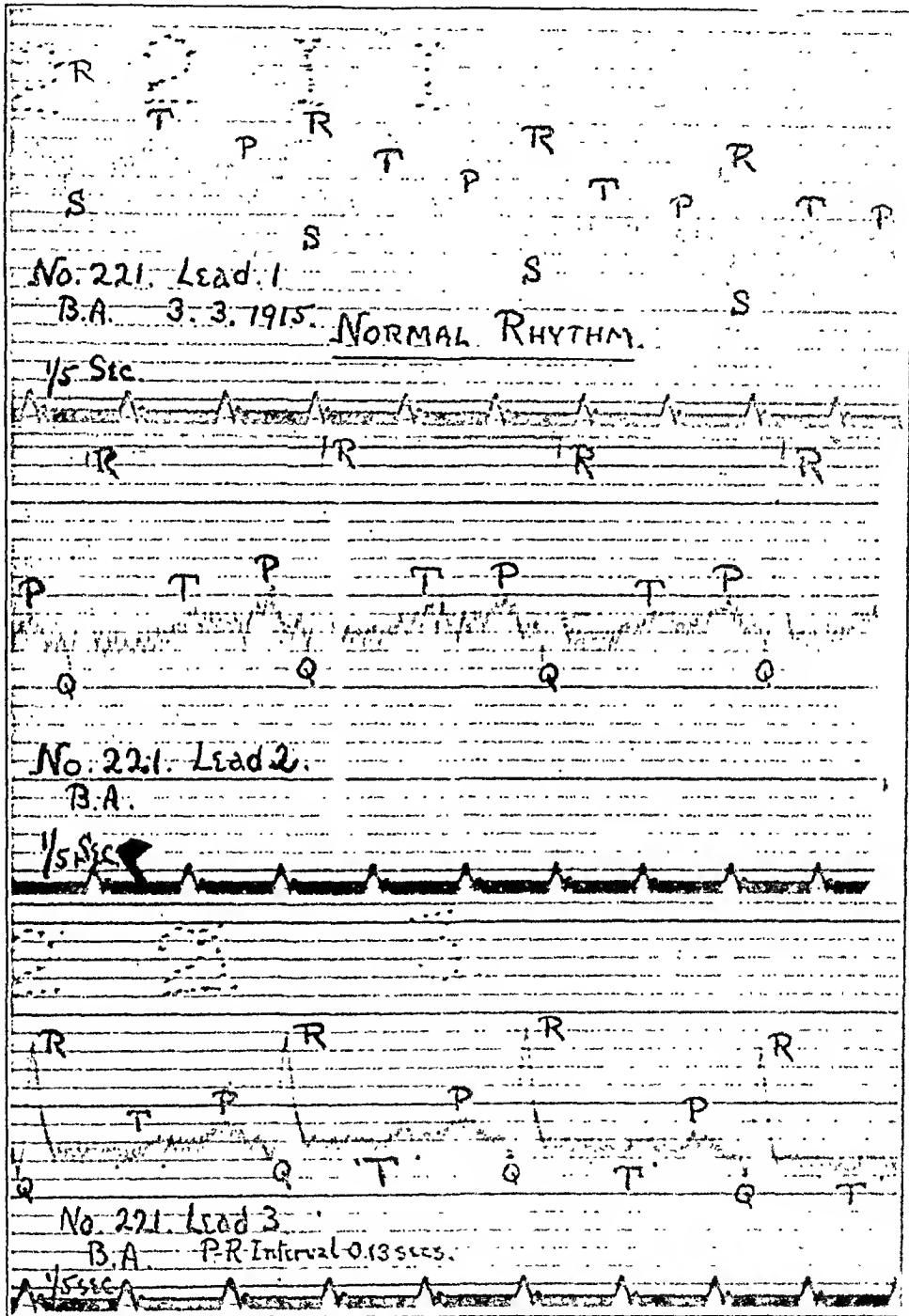


Fig. 5 (Case 2).—Electrocardiogram of same patient as in Figure 4, taken March 3, showing normal rhythm.

to the left, the apex beat distinct in fifth space, 12 cm. from the mid-line. There was a distinct apical systolic murmur transmitted to the axilla, with accentuated second aortic and pulmonic sounds. An electrocardiogram (Fig. 4) showed the arrhythmia to be due to an auricular fibrillation of the

coarse type. With the fear of operation removed, and after a quiet night in bed, the patient awoke the next morning without any disagreeable subjective sensations, and the pulse was regular and much slower. The systolic blood pressure, which during the attack of fibrillation had been 165, was found during the period of regular rhythm to be 132. The diastolic fell from 85 to 78.

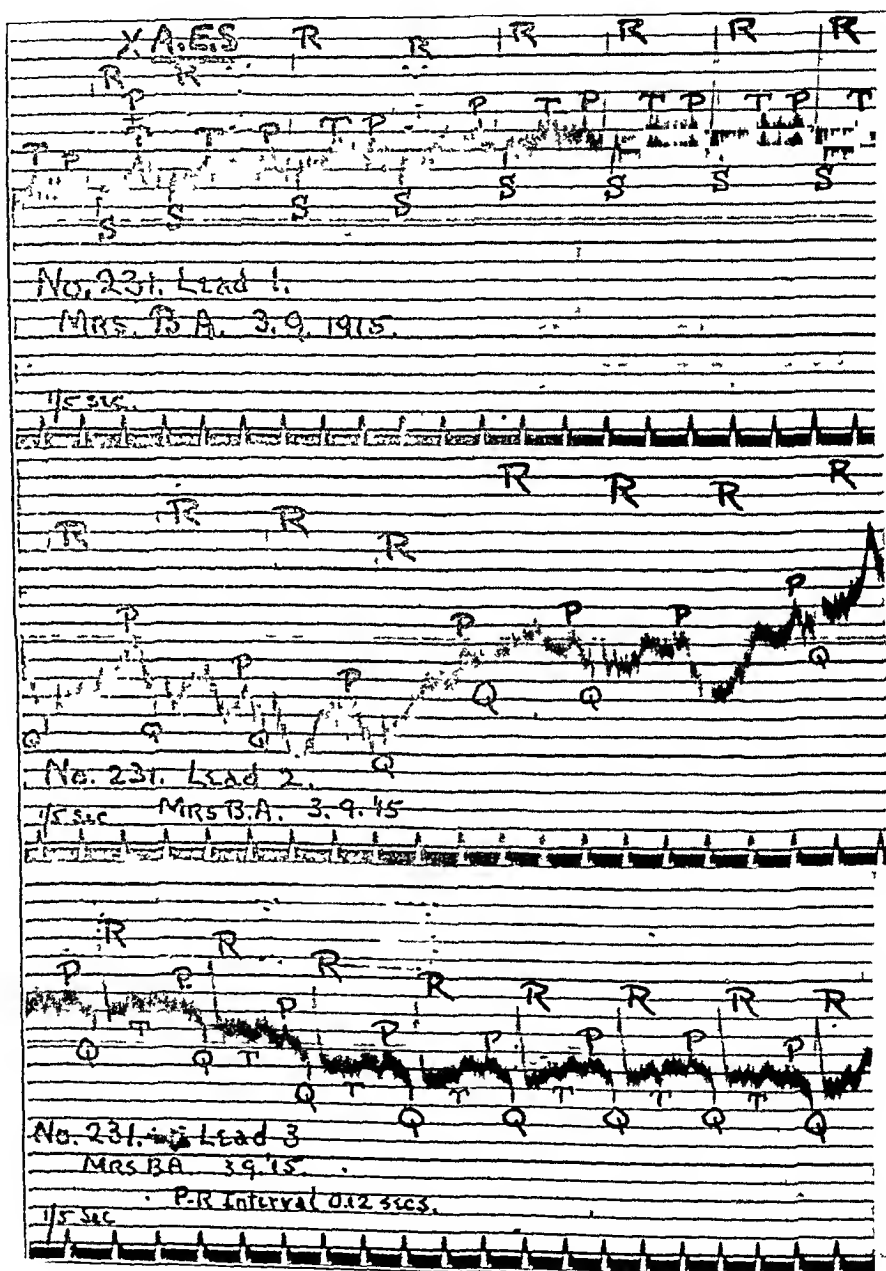


Fig. 6 (Case 2).—Electrocardiogram of same patient as in Figure 4, taken March 9, showing normal rhythm occasionally disturbed by an auricular premature contraction.

An electrocardiogram (Fig. 5) taken the same morning showed a regular rhythm, with a normal P wave. The complexes were practically the same as in the former record (the more rapid passage of the film being shown by the increased intervals of the time marker), except that systole (as indicated by

the end of T) lasted more than 0.3 second and was immediately followed by the next P wave. For several days the patient's improvement continued, the pulse being either quite regular or showing only an occasional slight irregularity. The nature of this irregularity is shown in Figure 6 to be due to an occasional extrasystole. Although there is practically a complete compensatory pause, this is probably an auricular extrasystole merging with the preceding T, because the following ventricular complex shows no ectopic origin.

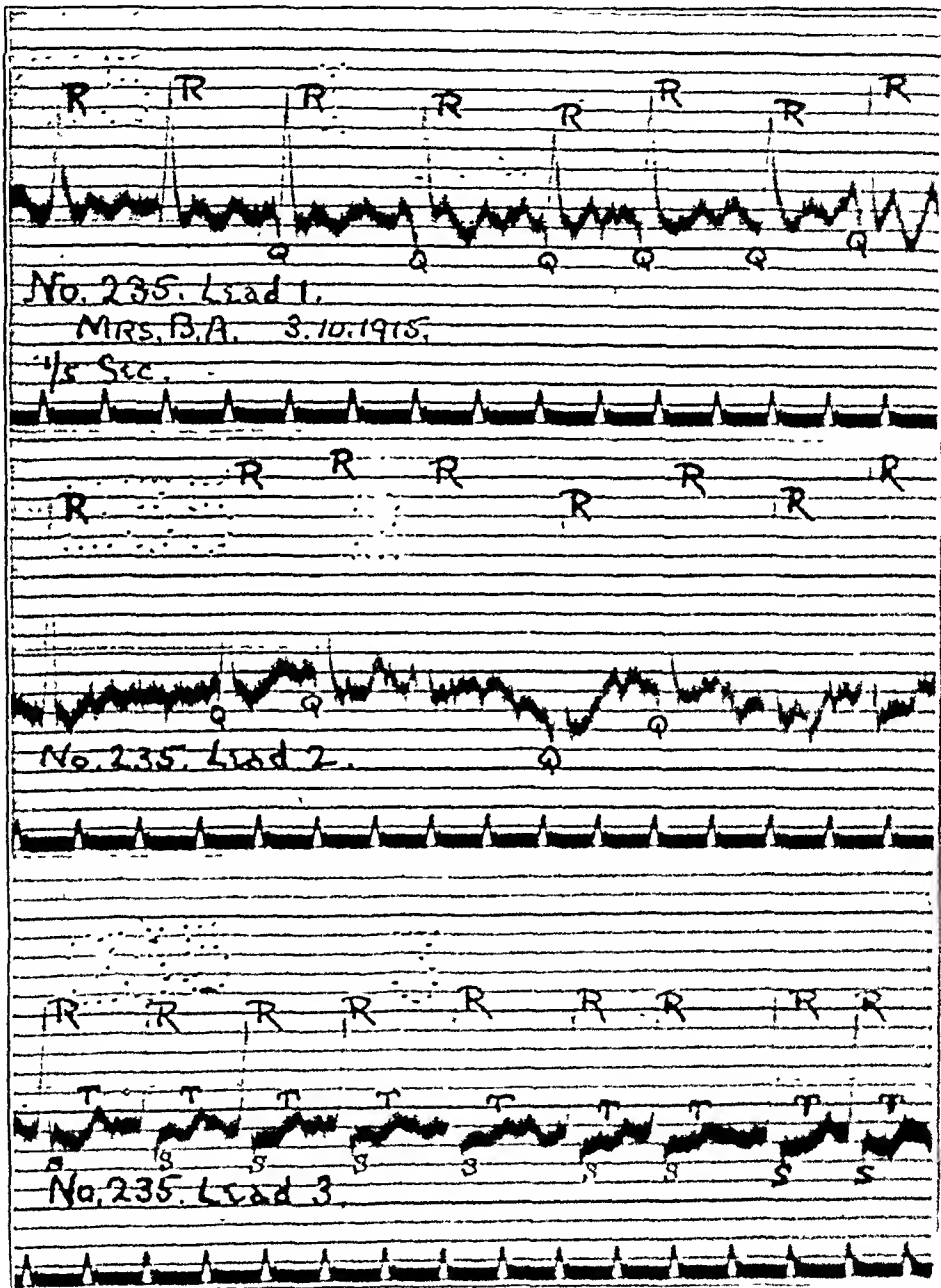


Fig. 7 (Case 2).—Electrocardiogram of same patient as in Figure 4, taken March 10, showing another period of transient auricular fibrillation.

After one week's improvement, the patient awoke one morning from a terrifying dream, and felt her heart pounding violently. Auscultation disclosed a total arrhythmia, with disappearance of all murmurs, a cardiac rate of 130, and a pulse deficit of 50. The systolic pressure was found to have risen to 155, the diastolic remaining at 70. An electrocardiogram (Fig. 7) showed that

coarse fibrillation had again supervened. In Lead I, especially, the fibrillatory waves were so marked and regular that at first the condition of auricular flutter was suggested. This was rejected, however, as the rhythm of the waves of fibrillation was not absolutely regular and the ventricular response was totally irregular, and not explainable by any combination of heart block. During the same afternoon, the patient suddenly announced that the trouble had stopped, and the rate was found to be much slower (80 per minute) and less irregular. Occasional extrasystoles, however, persisted for forty-eight hours. After one week of normal heart action, the patient was returned to the surgical wards for myomectomy and from this time on she flatly refused to allow further cardiac examination.

It is of interest that the patient later volunteered the information that she had had a strong psychic disturbance before each cardiac attack. It is of course possible for a third and unknown factor to have been responsible for both the nightmare and the paroxysmal attack of fibrillation, but the presumption is strong that the cardiac attack was induced by nervous excitement. The chronic endocarditis, enlarged heart and positive Wassermann would all indicate a basic myocardial involvement requiring only the nervous excitation to produce the paroxysm of fibrillation. The appearance of auricular extrasystoles for a few days after each attack is also of interest. It is impossible to say whether these also were of nervous origin or a sign of myocardial degeneration, but here again the time of their appearance affords a strong presumption that the psychic element was at least one factor in their production. A recent report, one year after the period of observation, states that the patient is now in a state of chronic decompensation and that the arrhythmia has become permanent.

Summary of Case.—In a highly excitable, nervous woman, on several occasions strong emotional excitement was observed to be followed by transient attacks of auricular fibrillation. Though the blood pressure was higher during the periods of fibrillation, the state of the pressure just preceding the attacks could not be determined. After the normal auricular activity had returned, the regular rhythm was disturbed for one or two days by occasional auricular extrasystoles. After repeated attacks during the next year, the fibrillation, which had a probable syphilitic myocarditis as a basis, became permanent.

III. TRANSIENT AURICULAR FIBRILLATION OF TOXIC ORIGIN

CASE 3.—W. W., a white man, single, aged 40 years, was referred to me for examination on Oct. 12, 1915, by Dr. Newlin, on account of extreme palpitation, dyspnea and arrhythmia of two days' duration. One brother had died of heart disease, following over-indulgence in alcohol, and there was a general family tendency toward overeating and overdrinking. Except for occasional attacks of tonsillitis, the patient had not had any severe infections, but had always eaten too much, and had been a steady consumer of alcohol, but seldom to the point of intoxication. For years he had had some distress after eating and had occasional attacks of heartburn. He had always considered himself in excellent health, however, had not overworked, and had been able to undertake violent exercise without the slightest embarrassment.

The present illness began two months previously while the patient was on a hunting trip in the Rocky Mountains (altitude 5,000 feet). Following an attack of acute bronchitis, the patient noticed that he easily became dyspneic and tired, and that his heart occasionally "skipped" beats. The trip was abandoned, and with appropriate treatment the symptoms disappeared. Systolic blood pressure at this time was 150. In three weeks' time the patient felt

entirely well, except for a mild afebrile tonsillitis, which persisted for several weeks. On a carbohydrate-poor diet he succeeded in losing 50 pounds and the systolic blood pressure dropped to 140. He then began three days of increased alcohol consumption, and became nervous and irritable for several days, but without cardiac symptoms. Then without adequate explanation, after one week of total abstinence, extreme palpitation and arrhythmia developed, with dizziness on standing. The systolic pressure at this time was only 110, diastolic 90. This attack had continued for the two days immediately preceding his visit to the hospital, but he had improved sufficiently to walk without distress.

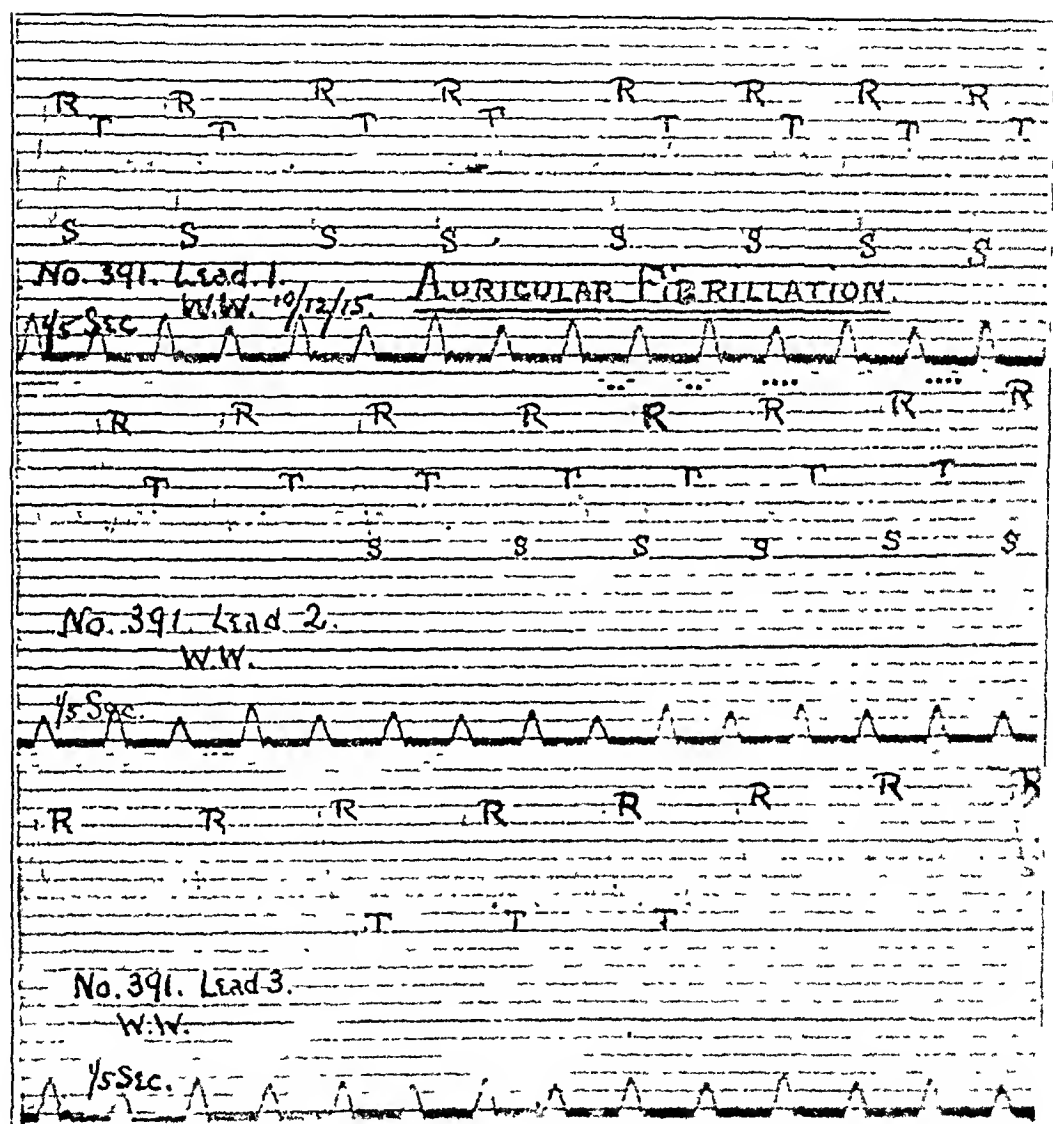


Fig. 8 (Case 3).—Electrocardiogram of patient W. W., who had no discoverable organic lesion, showing transient auricular fibrillation of toxic origin.

Physical Examination.—The patient was a large, powerful, well-nourished man, weighing 258 pounds. Although normally rather lethargic, he was at that time apprehensive and slightly dyspneic. The eyes were negative. The tongue was moderately coated, the tonsils red and swollen, but without exudate. There were irregular heavings of the neck, but no distinct venous pulsation. The pulse rate was about 120 and very irregular in force and rhythm. The vessel wall was indefinitely palpable. The heart rate by auscultation was 160, also irregular in force and rhythm, giving a pulse deficit of 25 per cent. The

apex beat was not visible or palpable; the cardiac dulness extended to the right border of the sternum in the fourth space, and 1 cm. to the left of the midclavicular line at the fifth space. No murmurs were audible, but the muscle sounds were rumbling and of poor quality. Examination of the lungs and abdomen was negative. The legs showed very slight pitting on sustained pressure. Frequent urine examinations were always negative.

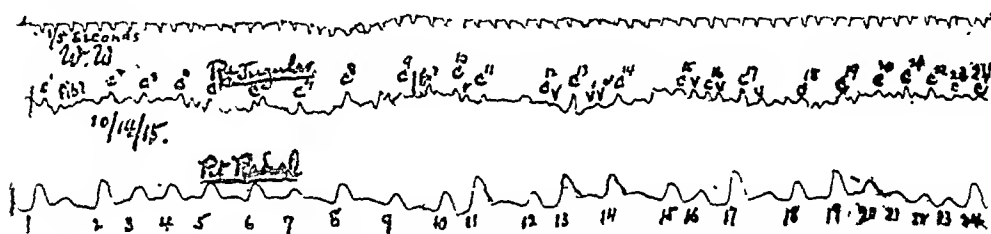


Fig. 9 (Case 3).—The polygram taken immediately after the electrocardiogram shown in Figure 8 exhibits in a more marked degree the irregularities of force and rhythm. The unmarked "c" waves of the jugular pulse indicate the amount of pulse deficit.

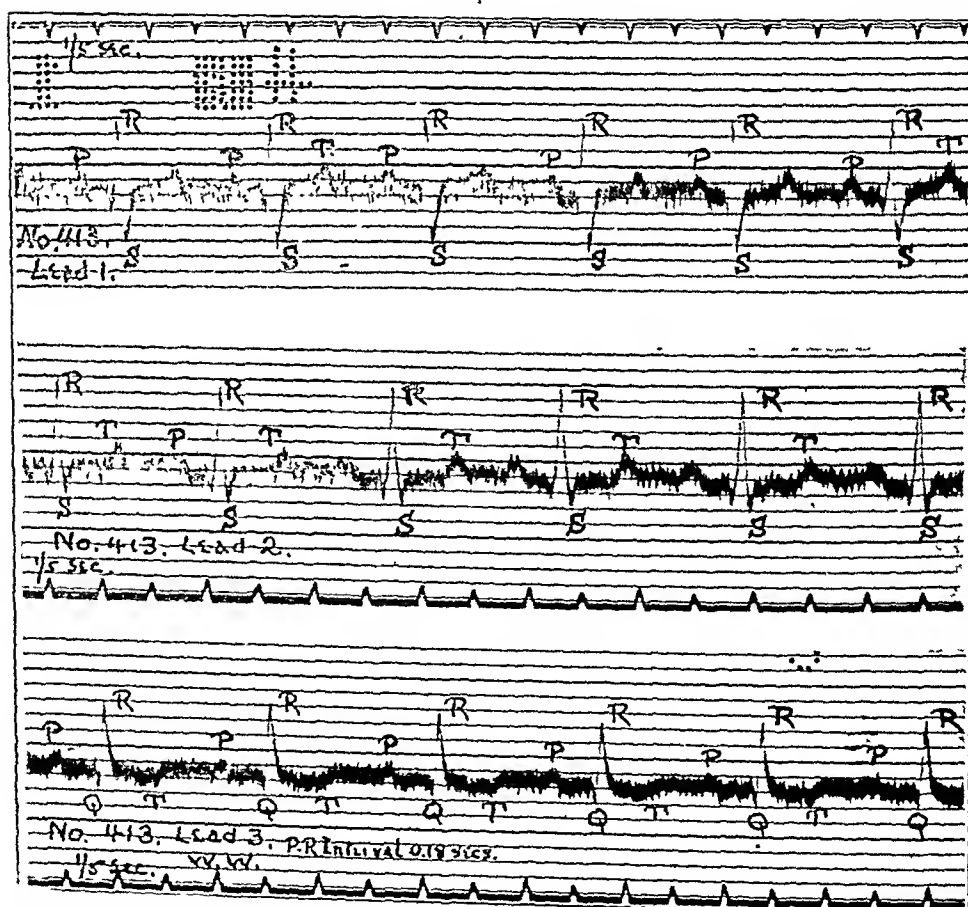


Fig. 10 (Case 3).—Electrocardiogram of same patient as in Figure 8, taken three weeks later, showing normal rhythm.

After three days' treatment, consisting of digipuratum (0.1 gm. four times a day) and local applications to the tonsils, the patient's condition was greatly improved, with cessation of palpitation, dyspnea and cardiac distress. This

was confirmed by Dr. Newlin, who found the heart action and sounds normal and no pulse deficit. The systolic blood pressure was 120 and the diastolic 80. As a result of this improvement the patient resumed his former habits of over-eating and overdrinking and in seven months had another cardiac attack lasting three days, which again responded to digitalis. This attack occurred in the middle of the night, while the patient was trying to induce vomiting for the relief of an attack of heartburn. At the present time (May, 1916) he has headaches, gets tired easily, and does not feel so well as before the first attack.

An electrocardiogram (Fig. 8) taken on the patient's first visit showed a distinct arrhythmia with absence of the P wave and with the coarse type of auricular fibrillation. The delirium cordis, however, was much more strikingly shown in the polygraph (Fig 9) taken at the same time, although by this time the patient felt much better and could not say whether or not his heart action was irregular. An electrocardiogram (Fig. 10) taken three weeks later showed a normal regular rhythm with well-developed P wave. The form of the ventricular complex is but little changed from that of the former record.

Summary of Case.—In an adult man, without previous signs of cardiac disease, but with a history of heartburn and chronic overindulgence in food and alcohol, signs of slight cardiac decompensation developed three months before observation. After a short period of improved health, auricular fibrillation with marked cardiac symptoms developed without apparent adequate cause. This persisted for three days, but disappeared under appropriate treatment of rest, digitalis, and local treatment of a subacute tonsillitis, and up to the present time (eight months) has not reappeared, except for one other transient attack lasting for three days. An underlying myocardial weakness is probably in this, as in the other cases discussed in this series, an important factor. While it is impossible absolutely to identify the determining cause of the attack of fibrillation, the blame most probably must fall on either alcohol or the subacute tonsillitis. There were very few signs of decompensation at any time and with the removal of the sources of intoxication, the fibrillation ceased; and yet on account of the probable myocardial disease, a recurrence with correspondingly grave prognosis, must be considered as probable.

IV. TRANSIENT AURICULAR FIBRILLATION DURING DECOMPENSATION IN PANCARDITIS

CASE 4.—J. P., a white man, single, 18 years old, was admitted to the hospital Feb. 16, 1916, during an attack of severe decompensation, superimposed on chronic valvular disease, cardiac hypertrophy and chronic nephritis. The chief complaints were dyspnea, cough, edema of buttocks and extremities. Although cardiac symptoms had been present only four years and then occurred without determined adequate cause, it is probable that the cardiac disease started during a severe undiagnosed illness in infancy, which lasted eight or ten months. He also was said to have had measles three times during childhood, but his past history and family history is otherwise negative. Although he had had two or more attacks of decompensation before this, he was "passed" by a railroad physician two and one-half years before. The patient presented the usual signs of a decompensated heart disease of long standing, with full face, bulging precordium, distended veins, tender liver, ascites and right-sided hydrothorax. His heart was enlarged both to the right and to the left.

a loud double mitral murmur was audible with an accentuated second pulmonic sound. The systolic blood pressure varied between 110 and 132; the diastolic between 93 and 110. The venous blood pressure equaled 14 cm. (water). The urine has always contained a large amount of albumin and

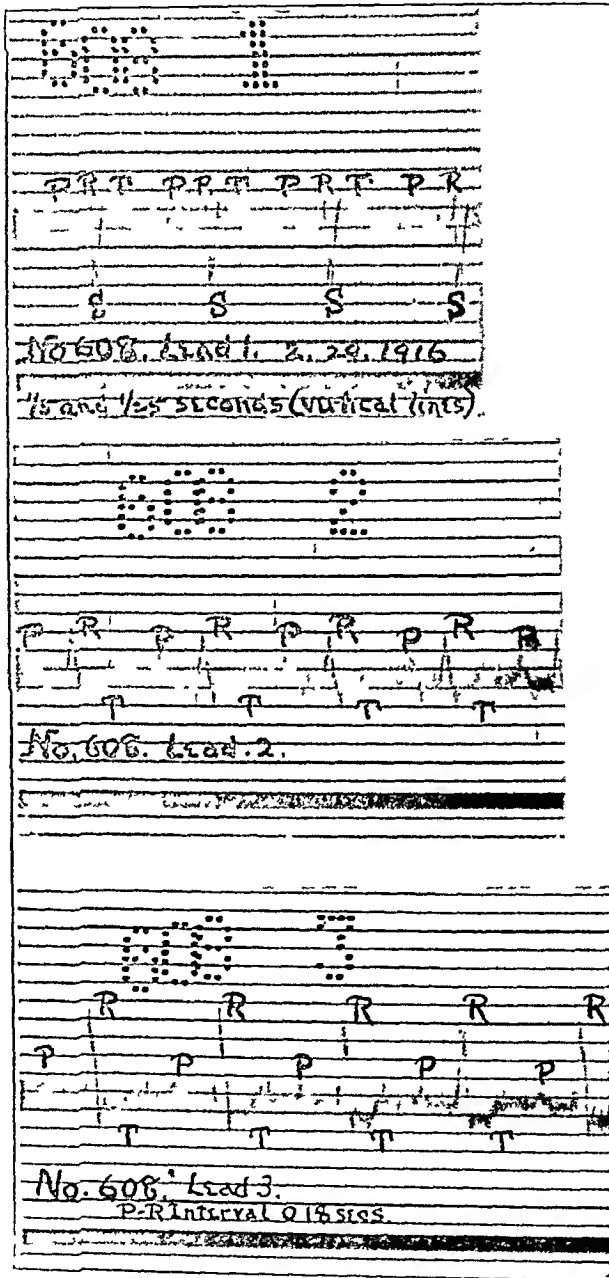


Fig. 11 (Case 4).—Electrocardiogram of patient J. P., a case of fatal mitral stenosis with decompensation, taken Feb. 29, 1916, showing normal rhythm, with right ventricular preponderance.

occasional hyaline casts. The phenolsulphonephthalein elimination was 40 per cent. The blood counts were normal. The Wassermann reaction was negative. An orthodiagram showed increase of cardiac shadow both to the right and left.

An electrocardiogram (Fig. 11) taken the day after admission showed a regular rhythm with well-defined P wave, and the evidences of preponderating hypertrophy of the right ventricle; the P-R interval was 0.18 second. In spite of absolute rest in bed, digitalis and codein medication, the patient's

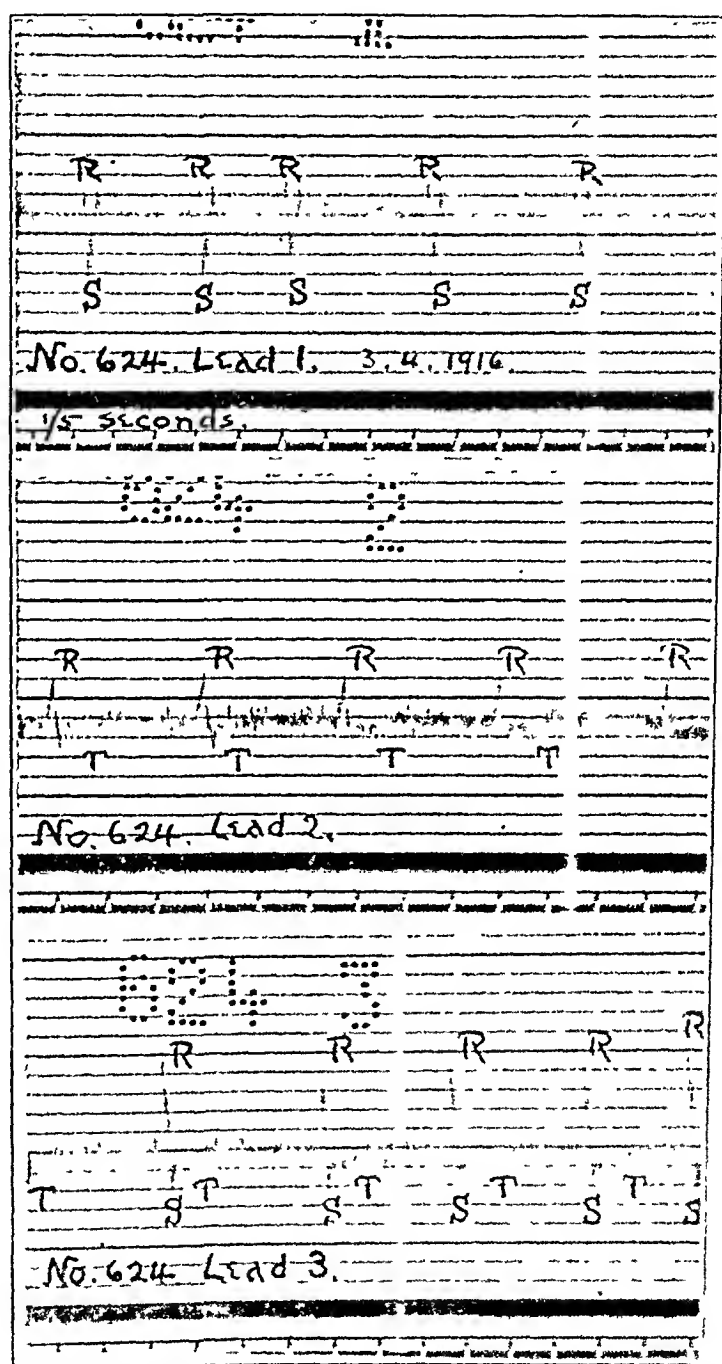


Fig. 12 (Case 4).—Electrocardiogram taken March 4, 1916, of same patient as in Figure 11, showing transient auricular fibrillation. Though the fibrillation has not been of long duration, the waves of fibrillation are not visible.

condition became steadily worse, with increased edema, insomnia, nausea and vomiting. An electrocardiogram (Fig. 12) taken twelve days later failed to show any change, and did not show any of Cohn's digitalis effects. A third record (Fig. 13), taken four days later, revealed the presence of auricular fibrillation.

although no arrhythmia was suspected until the prints of this record became available for study. Another record was taken three days later and it was found that the rhythm had again become regular with reappearance of the P wave. The day before this record was made (that is, two days after recording auricular fibrillation) the signs of acute pericarditis (loud to and fro fric-

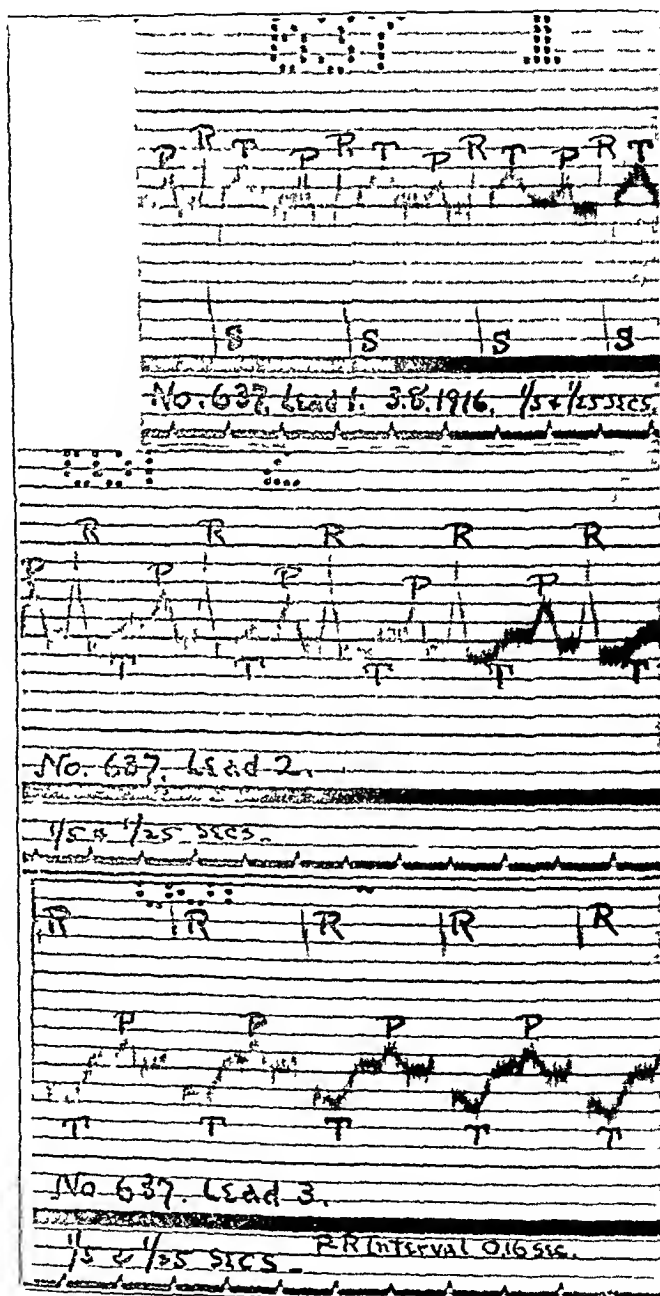


Fig. 13 (Case 4).—Electrocardiogram taken March 8, 1916, of same patient as in Figure 11, showing normal rhythm again, with large P Wave.

tion rub) became manifest, with increase in pulse rate (110 to 140), development of fever, and general aggravation of symptoms. Although these signs were definitely not present in an examination made the day fibrillation was determined, nevertheless an infection, not sufficiently advanced to cause signs,

cannot be ruled out as the added insult that provoked the auricular fibrillation. From this time on the patient became steadily worse, dying in four days from heart failure.

At necropsy the following conditions were found: Concentric hypertrophy of the right ventricle (weight 270 gm.); concentric atrophy of the left ventricle (weight 70 gm.); hypertrophy and dilatation of the right auricle, and concentric hypertrophy and chronic mural endocarditis of the left auricle; chronic mitral endocarditis (extreme stenosis and thickening, with sclerosis of chordae tendineae and tips of papillary muscles); acute fibrinous pericarditis, and (slight) acute vegetation mitral and mural endocarditis; chronic fibrous pleurisy and pericarditis (basal); general chronic passive congestion of viscera; hydrothorax (bilateral) and ascites. Histologic examination confirmed these findings and showed surprisingly little myocardial fibrosis.

Summary of Case.—A boy of 18, suffering with mitral stenosis, was admitted to the hospital in an extreme stage of decompensation, but with normal cardiac rhythm. His condition became steadily worse and eventually auricular fibrillation developed, and the next day an acute pericarditis was found to be present. Fibrillation was replaced after three days by normal rhythm, but death occurred four days later from cardiac failure with persistence of the acute pericarditis. At autopsy an extreme mitral stenosis, with cardiac hypertrophy and dilatation was found.

V. DEVELOPMENT OF PERMANENT AURICULAR FIBRILLATION

In two cases the onset of auricular fibrillation occurred while the patient was under observation. Although the first attack in each of these cases proved to be permanent, they are included in this series on account of certain prognostic indications that they offer.

CASE 5.—L. Z., a Polish woman, 33 years old, married, was admitted to the maternity ward of the University Hospital, Jan. 6, 1915, in her fourth pregnancy. The first three pregnancies were normal, but after the birth of the third child, she had a severe attack of "grippe," was in bed after that for three months, and was told by her doctor at that time that she had heart trouble. She had had scarlet fever, measles, chickenpox and typhoid as a child, but had never had sore throat, acute rheumatic fever, or any symptoms of heart disease. Her social and family histories were negative.

Her present attack of decompensation began about the seventh month and gradually grew worse as pregnancy progressed, until in the ninth month labor was induced by Dr. Hirst on account of extreme dyspnea and edema. After delivery her symptoms were much improved, but one week later an attack of intense dyspnea ensued, with precordial pain and a dry, nonproductive cough. She also suffered from anorexia, constipation, headache, weakness, and pain in both breasts (baby had been weaned two days before).

Physical Examination.—When transferred to the medical ward, the usual signs of marked decompensation were found. The pulse was regular, rapid, quick, fair volume and tension and the wall of the artery not sclerosed. The systolic blood pressure was 130, the diastolic 80. There were forcible arterial pulsations in the neck, with apparently the ventricular type of venous pulse. The cardiac impulse was forcible, 17 cm. from the midline (following curve of chest), almost in midaxilla, in the fifth interspace. The cardiac dulness extended 5 cm. to the right of the midline, 17 cm. to the left. At the apex the first sound was loud and preceded by a presystolic murmur and third a systolic

murmur also being heard nearer the sternum. The second pulmonic was accentuated, the liver enlarged and palpable and râles audible at the bases of the lungs. There was generalized edema, ascites and bilateral hydrothorax. The blood showed a moderate anemia. The specific gravity of the urine was 1.028, and it contained a cloud of albumin, and hyaline, granular and leukocytic casts. The phenolsulphonephthalein elimination was 47 per cent. The Was-

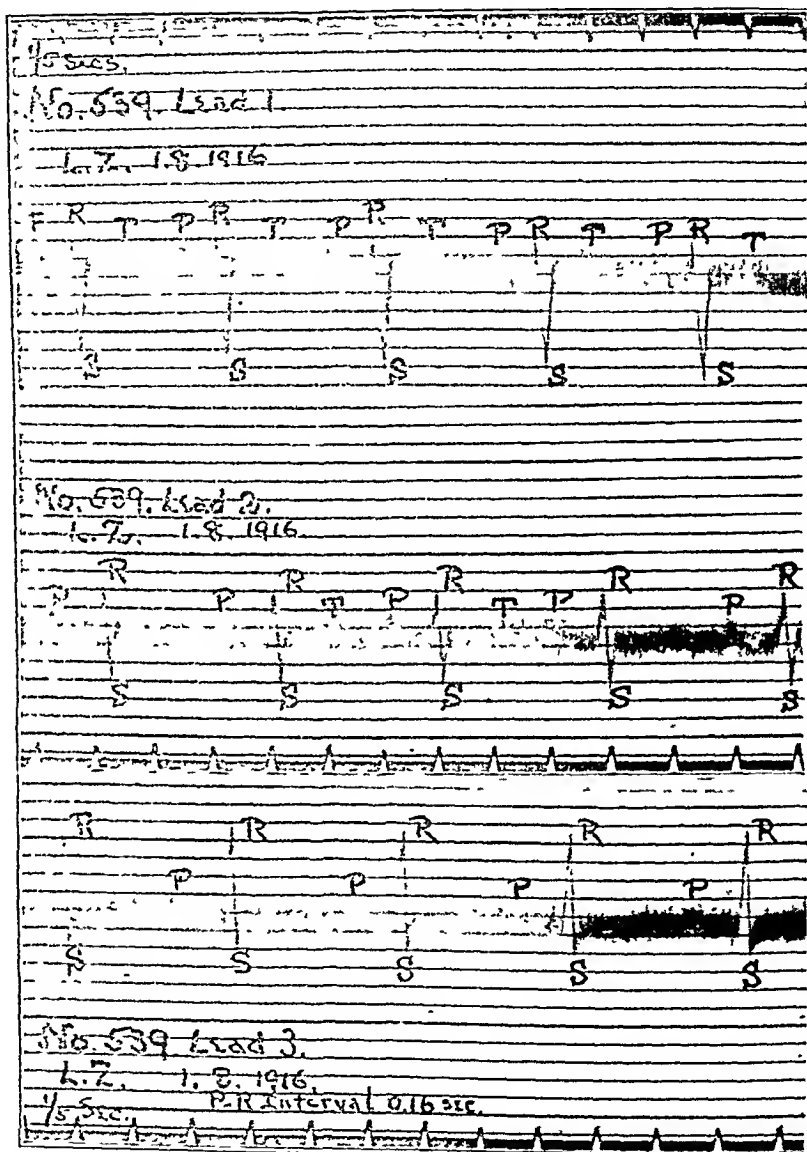


Fig. 14 (Case 5).—Electrocardiogram of patient L. Z., a case of fatal mitral stenosis with decompensation, taken Jan. 8, 1916, showing normal rhythm with right ventricular preponderance.

sermann reaction was negative. An electrocardiogram (Fig. 14) showed a regular rhythm with preponderance of the right ventricle and poorly defined T waves.

Course.—The patient improved slightly under digitalis and hypnotics, but four days after admission she had another attack of dyspnea and tachycardia. The pulse at the wrist was uncountable, the heart rate by auscultation was 196 and apparently regular. The following day, after a good night's rest, the

patient seemed much better and the pulse rate was lower. The day after this arrhythmia was first noted, and the electrocardiograph (Fig. 15) established the diagnosis of auricular fibrillation. Although there is no record of the heart rhythm on the intervening day, it is probable that the rapid period was due to auricular flutter, which progressed to fibrillation. The course of the physical signs and several electrocardiograms taken in the next few days

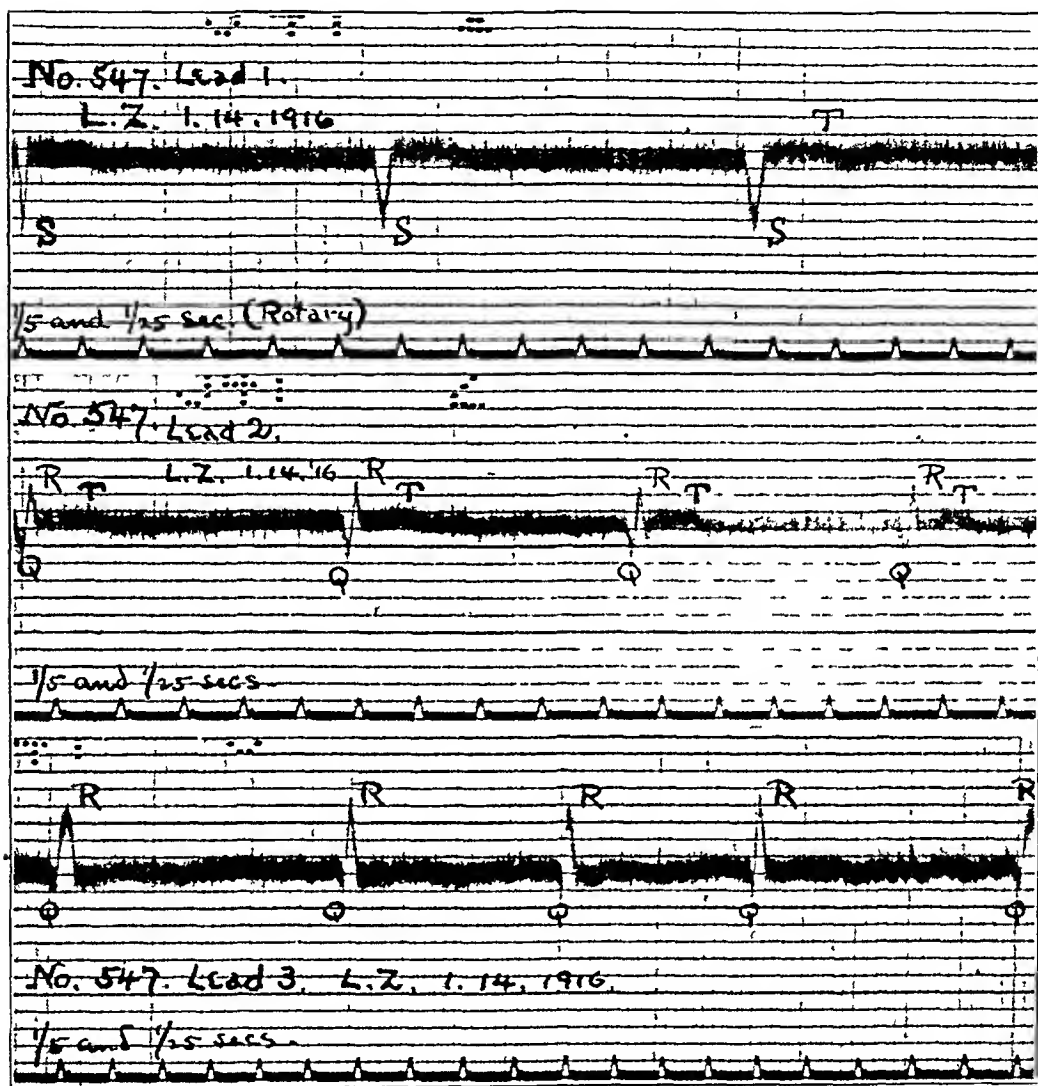


Fig. 15 (Case 5).—Electrocardiogram of same patient as in Figure 14, taken January 14, showing permanent auricular fibrillation. Though this symptom has not been of long duration, the waves of fibrillation are not visible.

confirmed the diagnosis of fibrillation and recorded the response of the heart to digitalis (slowing of rate, lessening of arrhythmia, change in form and Q and T waves). At no time were the waves of fibrillation of the coarse type. The patient, however, failed to improve clinically, and succumbed in three days with the signs of acute dilatation. Necropsy was refused.

Summary of Case.—A woman with mitral stenosis of at least four years' duration had such severe signs of decompensation during her fourth pregnancy that labor had to be induced. She improved during the first week of the puerperium, but then a second and more severe

stage of decompensation set in. In the third day of this attack a very rapid pulse rate was initiated (auricular flutter?) and this progressed to auricular fibrillation, which persisted until death three days later.

The development of auricular fibrillation after a transient period of flutter has been frequently observed; in fact the administration of large doses of digitalis has been recommended in cases of auricular flutter in the hope that the disturbance may pass on to fibrillation and thence, perhaps, return to normal rhythm. The contingency must at least be considered, therefore, in the present case that digitalis was a contributing factor to the causation of fibrillation.

VI. DEVELOPMENT OF PERMANENT AURICULAR FIBRILLATION DURING CARDIAC DECOMPENSATION

Another case is reported in which auricular fibrillation developed after three years occasional observation.

CASE 6.—M. H., an American woman, 35 years old, married, was admitted to the University Hospital on March 21, 1916, with the usual signs and symptoms of cardiac decompensation. This was a recurrence similar to those seen in her previous admissions in the spring of 1913 and the autumn of 1914. She had had measles, mumps, scarlet fever and acute articular rheumatism. Her cardiac symptoms were first noted at the time of a second attack of acute polyarthritis thirteen years before, and reappeared during an attack of "grippe" nine years before. For the past four years she has suffered from some shortness of breath and puffiness of the ankles, which on the two occasions mentioned became bad enough to make her seek the hospital. At both these times she improved quickly under hospital care, and she had never noticed any irregularities of her heart further than an occasional dropped beat.

The present illness started two weeks before admission with greatly increased dyspnea, palpitation and pericardial pain. Four days later the patient suffered a "stroke," losing the power of speech and of moving the left arm, but not becoming unconscious. Speech returned after sleep, but the left thumb, index finger and left side of the face have remained numb and weak. Four days after that, sudden pain developed low in the right chest with cough and hemoptysis, and the lesion was later shown by the Roentgen ray to be a pulmonary infarct. Social and family history irrelevant.

Physical Examination.—It was found on examination that the patient was more emaciated than on previous admissions; the tongue was dry and coated, with herpes on the lips. The cardiac dullness extended 3 cm. to the right of the midline and 13 cm. to the left. The apex beat was well localized in the fifth space 2 cm. outside of the midclavicular line. There was a harsh systolic murmur, best heard at the apex and transmitted to the base and axilla. No arrhythmia was noted. The liver was palpable 4 cm. below the costal margin and the right kidney was also palpable. There was dullness and râles at the bases of both lungs, but more marked on the right. The leukocytes varied between 10,000 and 14,000; hemoglobin 95 per cent., red blood cells 5,480,000. The urine was acid, specific gravity 1.018, contained a cloud of albumin, urates, but no casts. The Wassermann reaction was negative. The systolic blood pressure varied between 115 and 120, the diastolic between 77 and 90. The signs of decompensation decreased steadily during the patient's stay in the hospital, so that she was able to leave in one month in very good condition. The cardiac arrhythmia, which was first discovered by electrocardiographic examination, was still present, but frequently had been so slight that it could not be detected by simple digital examination of the pulse.

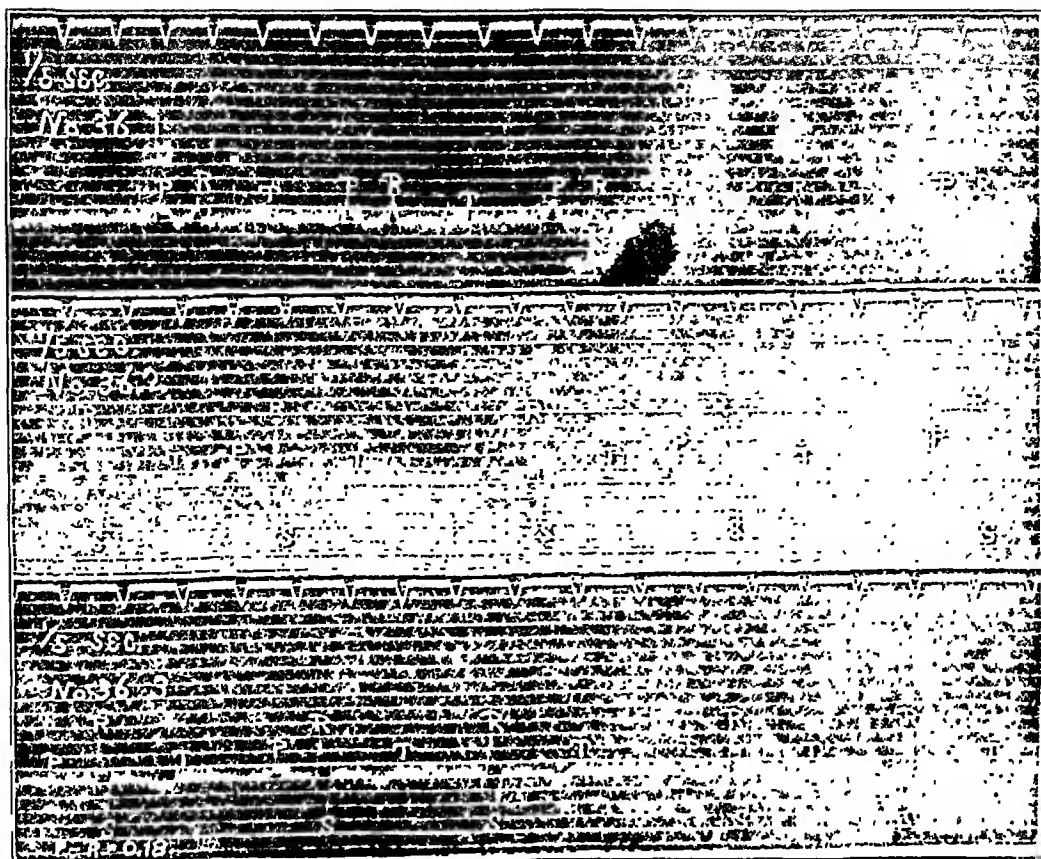


Fig. 16 (Case 6).—Electrocardiogram of patient M. H., a case of mitral stenosis with decompensation, taken April 14, 1913, showing normal rhythm (sinus arrhythmia).

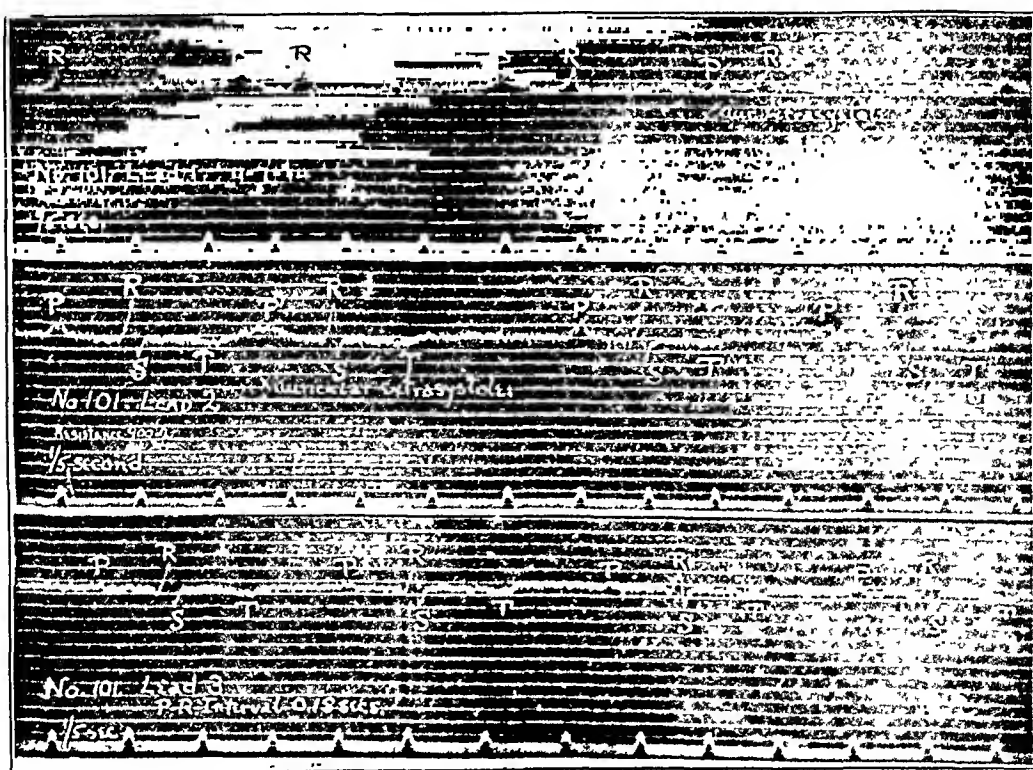


Fig. 17 (Case 6).—Electrocardiogram of same patient as in Figure 16, taken in November, 1914. The figure shows occasional auricular premature contractions.

Electrocardiograms (Fig. 16) were taken during each stay at the hospital. The one taken in 1913 showed a normal rhythm and complexes, with a P-R interval of 0.18 second. No abnormalities of rhythm were noted either during the examination or during the patient's stay in the hospital. The electrocardiogram (Fig. 17) taken in 1914 showed, besides some small changes in the form of the ventricular complex, the same P-R interval as on the first admission, but two definite auricular extrasystoles in addition. The large P wave

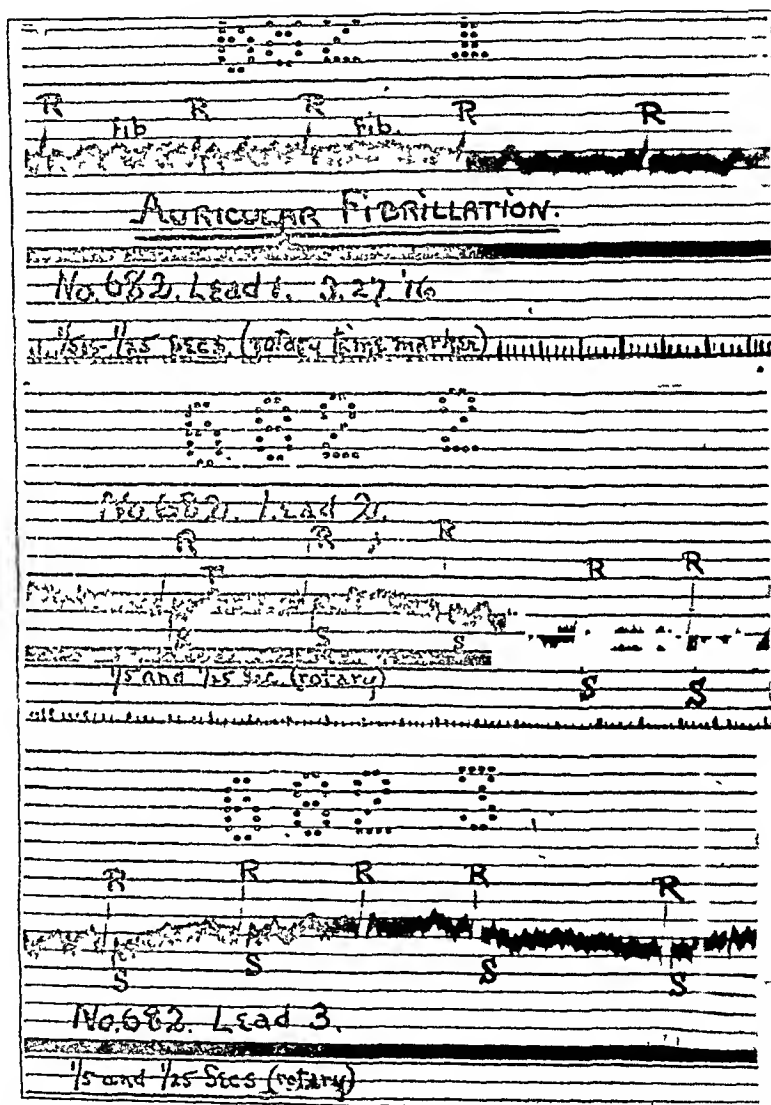


Fig. 18 (Case 6).—Electrocardiogram of same patient as in Figure 16, showing permanent auricular fibrillation (waves of coarse type).

characteristic of mitral stenosis persisted. On the patient's last admission in March, 1916, electrocardiograms (Fig. 18) taken on several occasions constantly showed a coarse type of auricular fibrillation. The form of the ventricular complexes, however, had changed very little from that of the two former admissions. Although the patient improved steadily from a clinical point of view, fibrillation persisted with a gradual decrease of the coarseness of the fibrillation waves.

Summary of Case.—In a case of mitral stenosis of some years' standing with recurrent periods of decompensation, electrocardiographic records were made over a period of three years. At first the rhythm was normal, next was broken by occasional auricular extrasystoles and finally was found to have been replaced by a constant, coarse type of fibrillation. If the history may be relied upon, this probably developed within two weeks of admission to the hospital, when decompensation was further complicated by cerebral and pulmonary emboli and infarct formation.

GENERAL COMMENT

A comparison of the foregoing cases with those mentioned in the literature allows the change from normal rhythm to auricular fibrillation to be subdivided into three types.

In the first group falls the first case of this series, twelve of Cohn's¹¹ pneumonia cases, all four of those reported by Fahrenkamp, Robinson's¹² recent case, the fourth of Heitz's and the sixth of Fox's series. In these cases the predominant factor was some acute infection or intoxication (pneumonia, septicemia, hyperthyroidism), and the attack of fibrillation was single. No organic cardiac lesion was found or need be presumed, and when the infection or intoxication was removed the rhythm returned permanently to normal.

In the second group, and this comprises the larger number of those cases reported as paroxysmal auricular fibrillation, belong the second and probably the third cases of this report, also the remaining nine of Heitz's, the four of Hornung's, four of Fox's series, and the single cases of Robinson, Popper, and Lewis and Schleiter. At the time of observation all but three of these patients were in the sixth or seventh decade of life, but the onset of attacks when mentioned occurred as follows: Two in the third decade, two in the fourth, five in the fifth, five in the sixth, and six in the seventh decade. The average duration of the condition was over nine years. Both sexes were equally involved. Previous diseases bore no relationship to the condition; even the cardiac condition varied greatly. In eight cases mitral lesions were present, but in ten others no valvular lesion was found. In nearly all; however, there was distinct evidence of myocardial disease. The blood pressure was found increased in seven and not increased in eight. Arteriosclerosis was noted in ten. Factors determining the paroxysms were either absent or widely varying in character. In six, emotional excitement preceded attacks and in two others they were attributed to a general increase in

11. Cohn, A. E.: Certain Phases of the Action of Digitalis in Pneumonia. Meeting of Am. Soc. for the Advancement of Clin. Investigations, Washington, D. C., May 8, 1916, unpublished.

12. Robinson, G. C.: Transient Auricular Fibrillation in a Healthy Man Following Hydrogen Sulphid Poisoning, Jour. Am. Med. Assn., 1916, lxvi, 1611.

the patient's nervousness. In four, attacks were induced by exercise or fatigue, but in three others they nearly always occurred during sleep. Overeating (three cases), defecation, and asthmatic attacks were held responsible in other cases. Many of these factors might be grouped under the head of conditions that raise blood pressure, but in some cases this factor was definitely absent. The duration of the individual attacks was also extremely variable, ranging from a few minutes to several weeks; in most cases, however, they lasted a few hours. In the early stages the attacks tended to be either short or infrequent, the duration and frequency of the attacks increasing as the disease progressed. They usually began abruptly, without premonitory symptoms, and caused more or less severe cardiac embarrassment. The attacks ended either during sleep or with such abruptness that the patient could notice the return to regular rhythm. In only one case were extrasystoles noticed between attacks, and in two cases there occurred also attacks of paroxysmal tachycardia. In this connection Lewis and Schleiter have called attention to the closely related mechanism of auricular extrasystoles, fibrillation and paroxysmal tachycardia. Six patients died while under observation (mostly from cardiac complications during regular rhythm); in five others fibrillation had become permanent; while six of the remaining ten were considered as improved. Venesection, digitalis and quinin have been used successfully and the ordinary treatment of cardiac failure seems advisable.

In a third group, represented by the last three cases of this report and the fourth of Fox's series, the onset of fibrillation should be regarded as but one more link in the chain of cardiac failure. In all these cases the signs of mitral disease with decompensation were prominent and had existed for years. In two cases the first attack of fibrillation proved to be permanent, one of these being preceded by auricular extrasystoles, in one other the permanent period was preceded by one transient period, and in the fourth a transient period lasting three days occurred a few days before death from cardiac failure (normal rhythm). The development of most of the cases of permanent auricular fibrillation is probably of this character, but closer observation and wider use of graphic methods would probably reveal one or more previous transient periods. As auricular fibrillation aggravates the prognosis, energetic treatment should be instituted at these times, in order to delay or avoid the onset of the permanent condition. That this should not include too large doses of digitalis is indicated by the fact that in two cases at least (Case 3 of this report and Robinson's case) digitalis was considered as a possible factor in the production of fibrillation. Its value as a cardiac remedy, however, especially after fibrillation is established, makes it a necessary aid in practically all such cases.

SUMMARY

Four cases are described in which the transition of the cardiac mechanism was observed from normal rhythm to auricular fibrillation and back again. In two others the development of permanent auricular fibrillation was observed. These have been compared with similar cases in the literature.

CONCLUSIONS

Transient auricular fibrillation is a comparatively rare condition, although the more widespread and frequently repeated use of the string galvanometer will probably reveal many more cases than are now available for study.

The change from normal rhythm to auricular fibrillation occurs in three well-defined groups:

1. In the course of an acute infection, such as pneumonia or septicemia, or of an acute intoxication, such as alcohol or hyperthyroidism, or possibly from other temporary causes, one or more attacks of fibrillation may occur for several days, but disappear permanently when the source of intoxication is removed. In this group permanent myocardial damage is probably not present.

2. In another group, probably always associated with underlying myocardial degeneration, paroxysms lasting from a few minutes to many hours or even days, may be induced by a great variety of causes and occur over a period of many years. They tend, however, to become more lasting or more frequent or both, and eventually with the progress of the myocardial disease the fibrillation becomes permanent. Death may occur, however, before permanent fibrillation has ensued, or clinical improvement may take place with the onset of fibrillation. The term "paroxysmal" is most aptly applied to cases of this group.

3. In a third group, in which the signs of valvular or myocardial disease are more prominent, the original change from normal rhythm to fibrillation is liable to be permanent, or at least be preceded by only a few transient periods. A determining factor in such cases is liable to be some cardiac complication, such as pulmonary embolus, acute pericarditis, or the added strain of pregnancy, and may be preceded by a transient period of flutter.

No relationship between the onset of fibrillation and changes in blood pressure could be established.

In the earlier stages of fibrillation the electrocardiogram usually shows coarser waves of fibrillation, so that this evidence, when present, may be guardedly used to influence favorably the prognosis.

The occurrence of fibrillation, while a bad factor in prognosis, does not necessarily indicate either permanency or a fatal outcome. It is of graver significance when it occurs in valvular cases with prominent signs of decompensation, and of least significance in the cases of the first group.

The usual treatment of heart failure (rest in bed, the digitalis group, removal of sources of intoxication, etc.) help to terminate attacks of fibrillation, but excessive doses of digitalis may help to induce this condition.

These cases were studied in the wards and laboratory of the University Hospital, while under the care of Drs. Stengel, Hirst, Anspach and Newlin, to whom my thanks are due.

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DISSOCIATED JAUNDICE *

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The subject of dissociated jaundice has been discussed by a number of French physicians during the past five years. There have been in all about thirty articles on the subject published in French medical journals. A fairly complete bibliographic reference will be found in an article by Lemièrre, Brulé and Garban.¹

In all the published articles there are several weak points for criticism. There was not sufficient correlative control of biliary elements in the plasma and urine. The adsorptive property of plasma for bile salts as well as bile pigment was not clearly perceived. As will be seen from our observations, the plasma may under some conditions, not yet clearly understood, retain a large amount of bile pigment and yield none of it to the kidney, although the kidney function may be perfectly normal. This adsorptive property of the plasma may hold bile pigment so firmly in its grasp that no pigment will be yielded to the tissues, so the disparity between icterus of the plasma and icterus of the skin may in some few instances be as striking as the disparity between cholemia and choluria. Adsorption of bile salts is not nearly so marked as adsorption of bile pigment, but in primary anemia, particularly, the presence of bile salts in the plasma without the presence of bile salts in the urine has been abundantly confirmed in our experience.

And, finally, without some improvement over the old method of separating bile salts from the plasma, it is impossible to make any progress in the clinical studies of jaundice. The older methods of separation were too time consuming, too uncertain, and required too much plasma for routine clinical work. The use of the collodion sack as a dialyzer affords a very simple, and we believe the most delicate, method thus far proposed for the purpose.

The term "dissociated jaundice" carries with it the inference that either the pigment or the salts of bile formed within the liver are separately shunted from the biliary path into the lymph or blood ves-

* Submitted for publication June 5, 1916.

1. Lemièrre, Brulé and Garban: Les retentions biliaires par lésion de la cellule hépatique, *Semaine méd.*, 1914, xxxiv, 301.

sels of the liver. We have succeeded thus far in showing that bile salts may be shunted in this manner, but we are not yet certain that bile pigment formed in the liver is separately shunted into the blood stream. This is what we should a priori expect when we consider the comparative facility with which the salts will pass through a dialyzing membrane, as shown by the concentrations of bile required to yield pigment and bile salts, respectively, to the dialysate when collodion sacks are employed for dialysis, and also when we consider the fact that the renal filter will yield bile salts to the urine from a lower grade of cholemia than is required for bile pigment to appear in the urine.

There have been several causes which have delayed the analysis of this very common problem in clinical pathology. Medical men generally have been for many years misled by the erroneous interpretations of jaundice made by Stadlerman and Naunyn and Minkowski, who arrived at the very definite conclusion that there can be no jaundice without the agency of the liver. According to these observers, all jaundice is hepatogenic, and hematogenic jaundice does not exist. Although many clinicians have been skeptical toward the teaching that all icterus is hepatogenous, the first satisfactory experimental evidence of the truth of hemolytic icterus I have found is that of Lyon-Caen,² 1910, and the final absolute proof of extra hepatic jaundice was given by Whipple in 1916.

Briefly stated, the following problems are to be solved in the clinical study of icterus. If pigmental cholemia is present without bile salts, the pigment may originate from the formation of bilirubin from hemoglobin within the blood vessels, as occurs in hemoglobinemia from any cause; or after complete cholemia of hepatic origin the bile salts have been yielded to the kidney and the adsorbed bilirubin remains fixed to the plasma. The latter instance is not dissociate jaundice of hepatic origin, but is merely separation of the two biliary elements by renal elimination of the bile salts. When bile salts without bile pigment are found in the plasma, we are bound by our present knowledge to assume there exists a genuine dissociate jaundice of hepatic origin. For thus far there are no clinical or experimental evidences to show there can be an extra hepatic origin of bile salts, and in all our experimental and clinical studies we find no evidence that bile pigment can be eliminated through the kidney and bile salts retained in the plasma. If the two biliary elements are separated by renal elimination, it will always be bile pigment which will be retained in the plasma and not bile salts. To avoid confusion in using the term "dissociation icterus" it will be advisable to employ a terminology which will indicate the source of the dissociation of biliary elements in the plasma. "Complete icterus" will mean the presence of bile pigment and bile salts in the

2. Lyon-Caen: *Jour. de physiol. et de pathol. gén.*, 1910, xii, 526, 758.

blood. "Hemolytic icterus" implies the presence of bilirubin in the blood without bile salts, when bilirubin is formed extra hepatically. "Hepatic dissociation icterus" implies the presence of bilirubin or bile salts separately in the plasma, due to one or the other of the bile elements being separately shunted into the blood stream. By "renal dissociation icterus" we mean the presence of bile pigment in the plasma due to separation of the biliary elements through renal filtration of the bile salts.

METHODS OF STUDY

The simplest and best method of detecting bilirubin in blood plasma is Gmelin's test. Between the white coagulum and the underlying nitric acid there is a yellow granular zone. Within the white coagulum there will be seen a line more or less broad, varying with the concentration of bile in the plasma, which has a distinct blue-green color. This blue-green line will appear immediately in high concentrations of bile, but in the very low concentrations of bile in the plasma the blue green line will not appear until after a lapse of half an hour. After the test has stood for a longer time, the white coagulum will ascend in the zone of plasma, but will always preserve the same thickness. The blue-green line holds its relative position in the white coagulum as this ascends, and the lower yellow zone increases in depth as the coagulum ascends.

The best method of detecting bile salts in the plasma we have found in the use of collodion sacks. A mixture of equal parts of alcohol and water is the best medium with which to surround the collodion sack containing the plasma.

In testing for bile salts we use two or three dialyzers, each containing about 5 c.c. of plasma. After the dialyzers have stood for twelve hours, the several dialysates are concentrated, and then the concentrated dialysate is tested with Pettenkofer's method. Simply the color test and spectroscopic absorption band in the purple can not be accepted as proof of the presence of bile salts. If no further criticism is employed, there is great danger of accepting a test as positive which is really spurious. We have adopted the plan of accepting as positive only those tests which give the characteristic color reaction to furfurol and sulphuric acid; then the spectroscopic examination of the reaction will give an absorption band in the purple. After the reaction stands for twelve hours or more a darker purple color supersedes the original pink reaction, and then spectroscopic examination will reveal a disappearance or diminution of the original absorption band in the purple and the appearance of a new, sharply defined band in the orange. The alteration in color on standing and the movement of the absorption band into the orange are essential to prove the correctness of a Pettenkofer test. The dialysate from many serums will give the original pink color

and purple absorption band, but when the reaction is allowed to stand, it will not change to the pink-purple color; neither will the absorption band move over to the orange. This further observation in the Pettenkofer test has saved us from making many errors in detecting bile salts in the plasma. Without this control we would have pronounced many tests as positive which were really spurious.

We find the collodion dialyzer to be a great aid in detecting bile salts. It is a very simple method and is much preferable to the old method of separating the bile salts from the protein by repeated precipitations and filtering and washing, which is practiced in the Hoppe-Seyler method. Much less serum is required for the process, and in the Hoppe-Seyler method the Pettenkofer reaction is the final test, just as we employ it with the dialysate from the plasma. The delayed spectroscopic control is applicable to the Hoppe-Seyler method of separation of the bile salts as well as in our method of separation by means of the collodion dialyzer.

We tried electrolytic dissociation to detect bile salts in plasma, but met with no success. The dialyzer is much simpler and much more delicate. To procure bile salts from a solution by electrolysis requires a much higher concentration of bile salts than we find in the plasma of jaundiced patients.

We have found the collodion dialyzer and the spectroscopic control of the Pettenkofer test equally important. Both these measures have been essential to our clinical analyses of jaundice. Without a satisfactory method of detecting bile salts in plasma no progress can be made toward a study of dissociated icterus.

A review of the literature on dissociated icterus will show how the want of a satisfactory method for isolating bile salts from the plasma has hindered the progress of clinical studies of jaundice.

BILE SALTS AND PIGMENT IN THE URINE

Hammersten's method is the most satisfactory means of detecting bile pigment in the urine. This is the method we always employ when any case is reported as a positive test for bile pigmentation in the urine. Bile salts in the urine have given us more trouble than in the plasma. Pettenkofer's test is not so satisfactory as Hay's sulphur test, which can be inspected most satisfactorily when viewed from underneath the surface of the urine by aid of an electric lamp held between the observer's eye and the specimen which is being examined. The sulphur test is very delicate and simple and gives unequivocal results. We did not go far in studies of cholemia and choluria before we were impressed with the striking inconsistencies between these two conditions. For instance, in primary anemia we have studied fourteen cases and we failed to find bile pigment or bile salts in the urine in a single instance,

although all the patients examined had bile salts or bile pigment or both in the plasma. It is surprising to see how high a concentration of bile pigment will occur in the plasma of primary anemia without choluria.

In hemolytic jaundice with infection and without infection it is also surprising to see how deeply jaundiced the plasma will become without bile pigment appearing in the urine. This is the one point which serves to distinguish obstructive jaundice from other sources of jaundice. In obstructive jaundice the bile pigment appears in the urine much more promptly and with much lower concentrations of bilirubin in the plasma than must occur in hemolytic jaundice before the urine becomes bile stained. We find an unvarying consistency in the behavior of bilirubin toward the collodion dialyzer (with rather thick wall) and toward the renal filter.

If a patient has bilirubin in his blood and none in his urine, the dialysate from his plasma will contain no bilirubin. If bilirubin occurs in both plasma and urine, the dialysate will contain bilirubin. We have had only one experience which was apparently an exception to this rule. The patient had severe hemolytic dissociated icterus caused by streptococcus infection. The plasma was deeply stained with bilirubin, but no bilirubin could be found in the urine. The plasma dialyzed bilirubin in large amounts. The disparity in this instance was traceable to a severe disease of the renal filter, as shown both clinically and at necropsy. During life the alveolar air had a carbon dioxide partial pressure of 26.7 mm. of mercury. The nonprotein nitrogen of the blood was 0.076 gm. per 100 c.c. of blood. The carbonates of the blood by Van Slyke's method were 37.9 c.c. per 100 c.c. of blood. It seems very reasonable in this case to ascribe the apparent exception to the rule to the impermeability of the renal filter.

When bilirubin from the plasma passes neither the renal filter nor the collodion sack, the phenomenon is due to adsorption of pigment by the plasma. We showed in one of our first clinical studies of a case of dissociated hemolytic jaundice due to secondary syphilis that the renal filter was unimpaired; not only was there a want of all evidence of impaired renal function on the part of the urine and blood, but at the same time the plasma was so deeply jaundiced as to give a very strong Gmelin's test and no bilirubin occurred in the urine, while the phenolsulphonephthalein test for renal function was perfectly normal. Unfortunately the phenolsulphonephthalein test was neglected in the streptococcus case, which gave us the single exception to consistency of behavior toward bilirubin on the part of the renal filter and the collodion sack.

The importance of adsorption of bile pigment in blood plasma is very significant in another phase of jaundice. We find the plasma deeply stained with bilirubin in some cases of primary anemia when

there is not only no bilirubin in the urine, but no trace of jaundice to the skin or sclera. This has occurred in several cases of primary anemia with complete cholemia and also in hemolytic dissociated cholemia. In several of these cases the cholemia was of such intensity that a like degree due to obstructive jaundice would invariably cause choluria and jaundice. From the pronounced disparity between cholemia, choluria and jaundice of the skin and the varying disparity in different sources for jaundice, it seems very clear that the degree of fixation of bilirubin to the plasma depends on some chemical alteration in the protein or lipoids of the plasma.

Furthermore, we are impressed with the fact that a large amount of bile pigment and also bile salts may be in the plasma and entirely disappear from the plasma without either salts or pigment making their appearance in the urine. *A priori*, we should say in view of all these facts that the plasma has the first call on the biliary elements and holds them with considerable tenacity away from the renal filter and in some instances away from the tissues also. This adsorption of bile pigment by the plasma readily accounts for the disparity generally seen between the concentration of bilirubin in the serum of ascitic fluid and pleural fluid and the subarachnoid fluid, on the one hand, and the concentration of bile pigment in the blood plasma in cases of jaundice, and it also accounts for the fact that large amounts of bilirubin may be found in the serum of fluid contained in the pleural cavity in cases of hemothorax without bilirubin appearing in the plasma of the circulatory blood. In other words, whether the bilirubin is adsorbed primarily to plasma within or without the blood vessels the plasma does not yield the bilirubin to the vessel wall any more readily than it is yielded to the renal filter or to the collodion sack. However, if we have a normal plasma and a normal liver the bile pigment and bile salts are readily yielded to the liver, as is clearly shown by animal experiment. The Gmelin test for bilirubin in plasma is not sufficiently delicate to give the blue-green zone in the coagulum when bile is added to the plasma in sufficient amounts to give a visible yellow stain to the plasma. So the best method is to compare the plasma of an animal, before the injection of bile into the blood, with the plasma after the injection into the vein has been made.

The concentration of bile varies greatly. In order to give us some conception of the pigment concentration of a specimen of bile and also to give some comparative idea of the quantitative value of bilirubin concentration in plasma, we record what proportion of bile or cholemic plasma must be added to a column of water 1 cm. deep to give a visible yellow tinge to the water.

When we refer to a specimen of bile as having a concentration of 1 to 100 or 1 to 3,000 and a specimen of cholemic plasma as having a

value of 1 to 20 or 1 to 100, we mean that that proportion of bile or plasma respectively must be added to a 1 cm. column of water to give a visible color.

Experiment 1.—Into the brachial vein of a dog weighing 17,000 gm. 40 c.c. of human liver bile were injected. This bile had a color value of 1 to 1,000. Estimating the circulatory blood in the dog at 1,300 c.c., we get a proportion of 30 to 1,000 of bile to blood. Oxalate plasma, procured by tapping the dog's heart five minutes after the injection of bile, had exactly the same color as the oxalate plasma procured immediately before the injection of bile. The plasma gave a negative reaction to Gmelin's test. Hueppert's test for pigment and the dialysate gave a doubtful reaction to Pettenkofer's test for bile salts. Five minutes after the first injection of bile, 40 c.c. more of bile were injected into the vein, and in another five minutes a third specimen of oxalate plasma was procured by tapping the cava. This plasma had a slightly jaundiced hue and gave a positive reaction for bilirubin to Gmelin's and Hueppert's tests and the dialysate gave a slight reaction for bile salts to Pettenkofer's test. The urine procured from the dog's bladder contained no biliary elements.

From previous experiments we found that after intravenous injections of bile the dogs had diarrhea with intestinal hypercholia. This suggested that the reason why the dog's plasma was not stained with bile was because the liver had the first call on bile pigment from the plasma when the plasma and liver were both normal.

Experiment 2.—Under scopolamin and ether anesthesia the abdomen of a dog weighing 13,000 gm. was opened and the superior mesenteric artery and the trunk of the portal vein were clamped to throw the biliary function of the liver out of commission. When this had been done 20 c.c. of human liver bile with a color value of 1 to 1,000 were injected into the femoral vein immediately after a specimen of oxalate plasma had been taken and found to contain neither bile pigment nor bile salts. Two minutes after the 20 c.c. of bile were injected a second specimen of oxalate plasma was taken. This specimen had a slightly jaundiced color and gave a positive test to Gmelin's reaction. There were neither pigment nor bile salts in the dialysate from the plasma.

Seven minutes after the first injection of bile a second injection of 20 c.c. was made and two minutes thereafter a third specimen of plasma was procured, which showed a distinct increase in the yellow color and a much stronger Gmelin reaction than in the preceding specimen.

When the liver was eliminated from the circulation, the animal's plasma was stained with bile about as one would expect it to be stained were the same concentration of bile in plasma made in vitro.

Experiment 3.—We then undertook to eliminate the liver, inject bile into the veins and then release the clamps on the superior mesenteric artery and portal vein to see how promptly the bile would disappear from the blood. From a dog weighing 6,500 gm., under scopolamin and ether anesthesia, specimen 1 of plasma was procured. The abdomen was then opened and the superior mesenteric artery and the portal vein were clamped. Then 30 c.c. of human bile, 1 to 1,000, the same as in Experiments 1 and 2, were injected into the femoral vein. Five minutes after the injection of the bile, Specimen 2 of oxalate plasma was procured, and five minutes thereafter Specimen 3 was taken. Then the clamps on the superior mesenteric artery and portal veins were released and the mesenteric and portal flow of blood were reestablished. During the procedure the pulse volume changed very little, so there could have been little change in the minute volume of blood through the heart and the hepatic artery. Five minutes after Specimen 3 was procured, Specimen 4 was taken. In five minutes more Specimen 5, and in ten minutes Specimen 6, of the plasma was procured.

The results of examination of the plasma gave:

Specimen 1, clear and colorless.

Specimen 2, clear, distinctly yellow; Gmelin's test positive; dialysate with faint color and bile salts positive.

Specimen 3, clear, yellow; Gmelin's test positive; dialysate with faint color; bile salts positive. The clamps on the artery and the vein were released.

Specimen 4, clear, slightly yellow; Gmelin's test negative; dialysate had no color; bile salts positive.

Specimen 5, clear, less yellow than 4. Gmelin's test negative; dialysate had no color; bile salts negative.

Specimen 6, clear, very slight yellow; Gmelin's test negative; dialysate had no color; bile salts (?).

We then proposed to see what results a temporary obstruction of the common bile duct would give in a comparative study of the biliary elements in the plasma and in the urine. In six trials we succeeded in getting one successful experiment, in which the catgut ligature on the common duct was absorbed and the path of the common duct reestablished, as was shown at necropsy on the dog. The common duct of a dog was ligated with catgut and nine specimens of oxalate plasma were procured by heart puncture from ten to 192 hours after the ligation of the duct. Each specimen of plasma was dialyzed. Seven specimens of urine were procured from twenty to 100 hours after the duct was ligated. The concentration value of the bile pigment in the plasma was determined. The Pettenkofer test for bile salts was employed in the dialysate from the plasma. In the urine Hammersten's test was used for bile pigment and Hay's test was used for bile salts.

The results on the plasma and the urine are shown in Tables 1 and 2, respectively.

TABLE 1.—EFFECT ON THE PLASMA OF LIGATION OF COMMON DUCT

Specimen	Time after Ligation of Common Duct, Hr.	Color	Gmelin Reaction	Concentration of Pigment	Dialysate	
					Pigment	Salts
1	10	None.....	0	0	0	0
2	28	Slight.....	+	1 to 50	0	+
3	48	More yellow.....	+	1 to 60	0	+
4	72	Increase.....	+	1 to 60	0	+
5	100	Less.....	±	1 to 50	Lost	Lost
6	120	Less.....	0	0	0	?
7	144	Very faint.....	0	0	0	?
8	168	Fainter.....	0	0	0	+
9	192	Still perceptible.....	0	0	0	+

From these results it is seen that in temporary obstruction of the common duct, although there was a marked cholemia for both pigment and salts, there was no choluria for bile pigment at any time, although bile salts continued in the urine during the entire period of 100 hours after ligation. At the same time there was marked pigment cholemia without pigment choluria. The dialysate from the plasma contained no pigment at any time, but always contained bile salts, as did the urine.

TABLE 2.—EFFECT ON THE URINE OF LIGATION OF COMMON DUCT

Specimen	Time of Ligation, Hr.	Bile Pigment	Bile Salts
1	20	0	0
2	28	0	0
3	36	0	+
4	48	0	+
5	72	0	+
6	96	0	+
7	100	0	+

The dog had a slight icteric hue to the conjunctiva, but the icterus was not marked and would have borne a doubtful interpretation in consideration of the fact the urine contained no bile pigment. If only the scleral icterus and urine had been considered, the picture would have been that of a dissociate jaundice in which bile salts were dissociated from bile pigment. The examination of the plasma, however, showed the dissociation was purely a renal dissociation, and not a hepatic dissociation.

Obstructive jaundice in patients may be interpreted as cases of hepatic dissociation jaundice, if the urine and plasma should be examined during a period of remission.

One of our patients had gallstones with jaundice. The plasma showed an abundance of bilirubin, 1 to 100, and a positive Gmelin test. The urine also contained bile pigment, but there were no bile salts demonstrable in the plasma or in the urine. There was no reason for suspecting a hemolytic jaundice and there were no evidences for hepatitis. The urine at the time of the observation contained only 1 per cent. of the total nitrogen in the form of ammonia, and no urobilin.

The plasma and urine were examined after an acute obstruction had subsided, and on this occasion we found only the adsorbed bile pigment, which was only a survival of a complete jaundice from obstruction. Had the findings in the plasma and urine been considered apart from the clinical history and physical findings, we should have interpreted the case as one of hemolytic jaundice, but when the previous removal of gallstone and prompt recovery from jaundice and the want of any signs of hepatitis were considered, it was quite apparent we were dealing with a renal dissociation of bile salts from the bile pigment which survived in the plasma in a state of adsorption.

Another case of gallstone lodged at the junction of the cystic and common ducts gave similar findings at one examination. When first examined the patient was icteric. The urine contained bile pigment

and bile salts. The plasma was icteric, 1 to 100, and gave a positive Gmelin test. The aqueous dialysate contained both pigment and bile salts in abundance. Fifteen days later the urine contained neither bile salts nor bilirubin and the plasma had a concentration of bile pigment of 1 to 50 and gave a positive Gmelin reaction. The water and alcohol dialysate from the plasma contained bilirubin, but gave only a doubtful reaction for bile salts.

The patient made a prompt recovery after the gallstone was removed by operation. In this instance we again have the renal dissociation of salts from bile pigment in the blood. The bile pigment survived in the plasma after obstruction which originally produced complete jaundice. The following case was apparently an obstructive jaundice attending an acute gastroduodenal inflammation:

The patient was a vigorous young man 21 years old, who came under observation on the third day of his illness, which began with nausea, vomiting, anorexia and jaundice, with a normal temperature. On entering the hospital, the liver was not enlarged or tender. There was moderate jaundice and the stools were clay colored. The mercuric chlorid test to the stool gave only a very faint reaction after standing twelve hours. The intestinal hypocholia was very marked. The duodenal tube was passed into the duodenum and gave only very slight evidences of bile in the duodenum. Microscopically the duodenal content revealed many epithelial cells and an abundance of bacteria. The stomach secretion contained no free hydrochloric acid. The urine contained an abundance of bilirubin and bile salts, but no urobilin. The oxalate plasma was jaundiced with a color concentration of 1 to 100, and Gmelin's test was positive. The aqueous dialysate contained much bilirubin and an abundance of bile salts. Eight days later the jaundice was much diminished. The duodenal contents showed a marked increase in the amount of bile. The urine contained no bilirubin and no bile salts or urobilin. The oxalate plasma still showed the same concentration of bilirubin, 1 to 100. Gmelin's test was strongly positive.

On this occasion alcohol and water, equal parts, were used for the dialysate and the dialysate contained both pigment and bile salts. This was an apparent exception to the rule that bilirubin in the plasma behaved toward the collodion sack as toward the kidney. But as we learned later in our experience that comparisons between the permeability of the collodion sack and the renal filter should be made with water as a medium around the sack and not with alcohol and water, this can not be regarded as a fair exception to the rule, namely, that bilirubin in the plasma has the same threshold to renal filter and collodion sack.

Thus far we are justified in saying that in obstructive jaundice there may be cholemia without choluria and also there may be a renal dissociation jaundice of the plasma if the blood should be examined at a suitable time after the retention of bile (from the liver) has ceased.

HEMOLYTIC JAUNDICE

The first patient with a clear hemolytic jaundice whom we studied was a woman who was profoundly anemic from a profuse hematemesis (ulcer). Transfusion was employed to combat the anemia. The husband acted as donor. Severe hemolysis followed the transfusion, as was shown by the chocolate colored urine, due to hemoglobin.

The following morning, twelve hours after the transfusion, the patient was observed to be icteric. The urine contained no bile pigment or bile salts. The oxalate plasma was icteric (1 to 60). The dialysate from the plasma contained no bilirubin or bile salts.

Another patient, a woman, who had always been in good health until an abortion was induced, which caused a streptococcus infection resulting fatally in ten days, entered the hospital with profound jaundice. On the day the plasma was examined the urine contained neither bilirubin or bile salts. The plasma was deeply jaundiced (1 to 275); Gmelin's test was very strongly positive. The aqueous dialysate contained neither bilirubin nor bile salts. The dialysate from alcohol and water contained bilirubin but no bile salts.

A man suffering from syphilitic myocarditis attended with general anasarca developed erysipelas on both thighs, where he violently scratched the skin with his finger nails. Within a few days after the onset of the erysipelas, the patient became icteric. The urine contained an abundance of bilirubin and no bile salts. The plasma was deeply stained (1 to 175). Gmelin's test was positive. The dialysate from the plasma (aqueous) contained bilirubin, but no bile salts.

The following case illustrates the behavior of bilirubinemia when the bilirubin is hemolytic in origin, but develops extravascularly.

A young man in perfect health received a stab wound of the left thorax four days prior to his admission to the medical ward of the hospital. A large amount of blood was found in the left pleural cavity, and 500 c.c. of the unclotted blood were withdrawn by paracentesis. The blood when centrifuged yielded only about 10 per cent. of its bulk in plasma. The blood did not clot on standing or after the addition of calcium. The plasma contained a small amount of oxyhemoglobin and a very large amount of bilirubin, and was not turbid. The bilirubin concentration was 1 to 450. Gmelin's test, also Huppert's and Hammarsten's test for bilirubin were strongly positive. The water dialysate from this plasma contained neither bilirubin, bile salts nor urobilin. The water and alcohol dialysate contained bilirubin, but no bile salts or urobilin. Blood from the patient's veins contained no bile pigment or bile salts and the urine contained no biliary elements.

This is a very striking instance of the adsorption of bile pigment in plasma. The concentration of bilirubin was much higher in the thoracic plasma than we have found in endovascular plasma in jaundice of any kind, and in spite of the very great accumulation of bile pigment in the intrapleural plasma no bilirubin was yielded to the collodion

dialyzer when water surrounded the sack. Some unknown change in the plasma occurs, to heighten its adsorptive power for bile pigment when blood escapes into a serous cavity in a healthy person.

In another patient who acquired a blood-serous exudate in the left pleural cavity on account of carcinoma of the pleura we found the same conditions of jaundice of the intrapleural plasma existed as in the case of traumatic hemathorax.

In none of our cases of obstructive jaundice did we find such a great disparity between pigmental cholemia and pigmental choluria as in our cases of hemolytic jaundice. When we speak of the threshold at which a concentration of bile pigment in the plasma will result in bile pigment appearing in the urine, however, it seems to us an error to regard this threshold as assignable to resistance offered by the renal filter to the passage of pigment. There is a wide variation of this so-called threshold, which can not be accounted for by varying renal function. The source of this threshold lies in varying adsorptive power of the plasma for bilirubin. On this basis we can account for the disparities which exist between the cholemia and choluria, and also for the varying disparities (in some patients) between the concentration of bilirubin in the blood and serous transudates, and the varying disparities between the jaundice of plasma and jaundice of the subarachnoid fluid; and finally for the varying threshold concentrations of bilirubin in the plasma toward the collodion dialyzer.

HEPATITIS

Hepatic dissociation jaundice in its relation to hepatitis is not clearly depicted in our experience. What constitutes hepatitis in many cases of acute infectious disease is not clear and should there be only bile pigment in the plasma and urine without bile salts, the question to solve is are we dealing with a dissociated pigmental jaundice of hepatic origin, or are we dealing with a hemolytic jaundice which is the result of the general infection? In other words, we are dealing with evidences of blood or liver deterioration as a result of infection. The question presents itself to us in this form, because thus far we have met with no instance of bile salts dissociation in the plasma of patients suffering from sepsis of any kind, or in patients with subacute or parenchymatous degeneration of the liver.

In two cases of pneumonia with jaundice we found only bile pigment in the plasma and no bile salts in either the plasma or urine. So there seemed very good reason for regarding the jaundice as hematogenous and not hepatogenous.

In two cases of acute infection we found large amounts of urobilin in the plasma along with bilirubin and bile salts. Great parenchymatous degeneration of the liver was proved in one of these cases at

necropsy and the other patient recovered after surgical drainage of a perigastric area of infection, which was due to a perforating ulcer at the pylorus.

In two cases of subacute hepatitis occurring in association with chronic interstitial hepatitis we were able to definitely ascribe the jaundice to a subacute hepatitis, and the plasma and urine both contained bilirubin and bile salts. In one case of chronic interstitial hepatitis, however, in which alcoholism and syphilis shared as etiological factors, the patient had an acute enlargement of the liver associated with jaundice. The patient was in the hospital three weeks. When he entered his plasma was icteric (1 to 100) and yielded bilirubin, but no bile salts, to the dialysate. The urine also contained bilirubin and much urobilin; bile salts were absent, and the stools contained an abundance of stercobilin. After a lapse of three weeks, during which time the jaundice diminished and all the other symptoms improved, the plasma was slightly icteric and gave bilirubin in the dialysate to alcohol and water, but no bile salts. The urine contained no bilirubin, bile salts or urobilin. These findings we must accept as a case of dissociated pigment jaundice of hepatic origin for the following reasons:

There was a moderate jaundice (1 to 100) and pigment was liberated through the renal filter and no salts were present in either the plasma or urine. Had there been complete biliary retention in the blood from a hepatic source, both the urine and the plasma dialysate would have contained bile salts or the urine would have contained bile salts before it would have contained bilirubin. This doubt may, however, be injected into the dissociation idea, namely, that the patient had complete jaundice before entering the hospital and renal dissociation of the bile salts may have been accomplished before he came under observation, as we saw him only during a period in which the pigment was a survival of complete jaundice. That we were not dealing with hemolytic jaundice is supported by the presence of a large amount of urobilin in the urine and the fact that bilirubin was excreted in the urine when there was only moderate icterus of the plasma. That we were not dealing with a residue from obstructive jaundice is attested by the abundance of urobilin in the urine and the abundance of stercobilin in the stools.

With the exception of this last case, we have not yet seen an instance in which we could seriously consider a dissociated pigmental jaundice of hepatic origin as a probability.

DISSOCIATED BILE SALTS JAUNDICE OF HEPATIC ORIGIN

Primary anemia affords some of the most striking characteristics of biliary elements in the blood. Of fourteen cases of primary anemia in which the plasma, urine and stools were examined for bile elements,

all but two showed bilirubin in the plasma and bile salts were present in large amounts in the dialysate from the plasma in both these cases. In none of the fourteen cases were either bilirubin or bile salts found in the urine.

In primary anemia we have seen the highest concentration of bilirubin in the plasma (without perceptible icterus of the skin or sclerae) which have come under our observation. It seems in primary anemia the fixation of bilirubin in the plasma is so firm that pigment is not only never yielded to the renal filter, but in some instances pigment is not yielded to the tissues when the plasma has a concentration of bilirubin as high as 1 to 150.

Of these two cases of bile salts dissociation, one, a man 52 years old, gave a history of having been ill for fourteen months. A few months prior to entering the hospital he had a marked lemon yellow color to his skin. On entrance there was no trace of icterus. Blood examination showed red blood cells, 2,312,000; white blood cells, 7,700; hemoglobin 70 per cent.; color index 1.5. A differential count gave polymorphonuclears, 67 per cent.; small mononuclears, 23 per cent.; large mononuclears, 7 per cent.; and transitionals, 3 per cent. The neurologic signs were very marked. There was a loss of both patellar and ankle reflexes, impairment of the vibratory sense in upper and lower extremities, and acroataxia and proximoataxia in both upper and lower extremities. The plasma was colorless and the plasma dialysate gave a reaction to Pettenkofer's test, which was strongly positive. The dialysate not only changed from cherry red to purple on standing twelve hours, but the spectroscopic examination showed that the movement of the absorption band on standing was from the purple into the orange. This was an instance of primary anemia. The patient formerly had pigment as well as salts in his blood, but during the period he was under our observation his blood contained an abundance of bile salts without pigment.

As to the other case of primary anemia which yielded salts from the plasma without pigment, there may be some doubt about the primary anemia. The diagnosis of primary anemia was made from the history of former anemia and the characteristic neurologic signs associated with degeneration of the posterior and lateral columns of the cord, with a normal cell count and negative Wassermann reaction on the spinal fluid. We regarded this patient as one who had recovered from his anemia with persistence of the neurologic symptoms. However this may be, the point of interest in this patient lay in the fact that bile salts were present in abundance in his plasma, as shown from the Pettenkofer test, with spectroscopic confirmation, and no bile pigment was found in the plasma or in the urine and no bile salts were found in the urine.

Two other cases of bile salts dissociation in the plasma were found in two cases of lead poisoning. Both patients had the characteristic lead line on the gums and both patients were exposed to lead poisoning. One was a house painter and the other worked in a storage battery factory. Neither patient had an anemia below 4,500,000 red cells and there was no icterus of the skin; neither was there any bile pigment or bile salts in the urine. The plasma in both cases was colorless, but the dialysate from the plasma in both cases gave a marked Pettenkofer reaction, which was confirmed by the change from a pink to a purple color, and the spectroscopic absorption band after twelve hours moved from the purple into the orange.

SUMMARY

1. We have found true dissociated jaundice of hepatic origin in two cases of primary anemia and in two cases of lead poisoning. In the four cases bile salts were found in the blood in large amounts, that is, the qualitative test for bile salts in the plasma dialysate was quite as strong as we find it in complete jaundice of pronounced severity.

2. Excepting in jaundice of hemolytic origin and in complete jaundice which has undergone renal dissociation, we have never found bile pigment without bile salts in the plasma.

3. Bilirubin and bile salts may both be present in very marked concentration in the plasma and neither pigment nor salts appear in the urine.

4. Adsorption of bilirubin in the plasma may not only withhold the pigment from the renal filter, but also from the tissues; so there may be pronounced cholemia (pigmental) without choluria (pigmental) and also without icterus of the tissues.

5. When pigmental cholemia is present (in varying degrees) without choluria, the collodion sack will yield no pigment to an aqueous dialysate from the plasma. When choluria attends cholemia (pigmental), the collodion sack will yield bile pigment to an aqueous dialysate from the plasma.

6. Bile salts will dialyze from plasma when no bile salts are demonstrable in the urine.

7. Without an examination of the plasma we are never justified in assuming that biliary elements have not been retained in the blood.

A COMPARISON, IN VARIOUS DISEASES, OF THE
CARBON DIOXID TENSION IN THE ALVEOLAR
AIR (PLESCH METHOD) WITH THE AMOUNT
OF CARBON DIOXID IN THE VENOUS
BLOOD (VAN SLYKE'S METHOD)*

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With the increasing interest among clinicians in regard to the amount of carbon dioxide in the blood and its relation to problems in respiration and acidosis, it is important, for the estimation of the carbon dioxide, to have methods which are applicable to most diseases and which may be frequently used in the same case.

Although previous to 1905 occasional observations had been made on the carbon dioxide content of the blood in animals and in man, by examination of the blood directly, a marked stimulus was given to this study on the introduction in 1905 by Haldane and Priestley¹ of a method for determining the content of carbon dioxide in the alveolar air. It is well recognized that the carbon dioxide tension in alveolar air corresponds closely to that of the blood in the arterial system.

Since 1905 different methods of collecting and studying the alveolar air have been devised by various workers. The results obtained by the different methods give slightly different figures. With some methods the carbon dioxide tension in the alveolar air corresponds to that in the venous blood, with others to that in the arterial blood. In 1914 Boothby and Peabody² compared the different methods of obtaining alveolar air from untrained subjects, and reached the conclusions that the Plesch³ method as modified by Higgins⁴ and slightly by themselves gave very constant results. This method depends on the ready diffusibility of carbon dioxide, so that after rebreathing a limited amount of air in the

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1. Haldane and Priestley: *Jour. Physiol.*, 1905, xxxii, 225.

2. Boothby and Peabody: *THE ARCHIVES INT. MED.*, 1914, xiii, 497.

3. Plesch: *Ztschr. f. Exper. Pathol. u. Therap.*, 1909, iii, 380.

4. Higgins: Publication No. 203, Carnegie Institution of Washington, 1915, p. 168.

closed system for a certain time the carbon dioxid tension is uniform throughout the closed system. Therefore the carbon dioxid tension in the air in the collecting bag is the same as that in the alveoli. This in turn is the same as that in the venous blood, since there is no opportunity for the escape of carbon dioxid. Of course, in this test the time allowed for breathing into the closed system is important, in order to avoid a heaping up of carbon dioxid above what was in the venous blood at the start of the rebreathing.

Boothby and Peabody tried out this method in a variety of diseases, and on patients who could not always cooperate with them. Nevertheless they obtained very consistent results. One of us during this past winter has been working with this method of determining the carbon dioxid tension in the alveolar air in a variety of different diseases. In many of these cases the respiratory rate was elevated. In others the patients were unable to cooperate in the technic advised for the collection of the air sample. It seemed desirable therefore to check up these results with the determinations obtained by a direct study of the venous blood for its carbon dioxid content. Such an opportunity was offered by the method recently devised by Van Slyke⁵ for the study of the carbon dioxid tension in blood taken directly from the vein.

This study has consisted therefore in a comparison of the results obtained from the determination of the carbon dioxid tension in the alveolar air and the estimation of the carbon dioxid tension in the venous blood as figured from a determination of the total carbonates in this blood. For the former the Plesch-Higgins method was used and for the latter that devised by Van Slyke. The studies were carried out on a variety of diseases, in which various degrees of severity were represented. The specimens of both air and blood were collected at approximately the same time, two or more hours after eating. If any slight interval did occur between the collection of the air and blood, care was taken to see that the patients did not receive any food or fluid in the interim.

The air was collected in the apparatus as described in detail by Boothby and Peabody.² The rubber bag was filled with 1,000 c.c. of air before the breathing began. Although it was impossible in many cases to adhere even closely to the prescribed five breaths in the twenty-five seconds allowed for breathing into the closed system, care was taken in all cases to preserve the exact limit of time. In all cases, except those in which the breathing was quite deep, effort was made to have the patient increase slightly the depth of the respirations. From each patient three separate samples were collected each time and

5. Van Slyke: *Jour. Biol. Chem.*, 1916, in press.

6. Haldane: *Methods of Air Analysis*, London, Charles Griffin & Co., Ltd., 1912.

then analyzed by the Haldane⁶ method for gas analysis. Usually these three samples varied from each other less than 2 mm. of tension, and an average of the three was taken. Occasionally one of the three showed considerable variation, in which case the one that showed the variation was left out of the reckoning. If one differed considerably it always showed an extra low tension, and presumably was due to some slip in the technic in obtaining the sample.

The blood for the Van Slyke test is drawn directly from a vein into enough potassium oxalate to make 1 per cent. or less of the amount of blood. It is then immediately centrifugalized and the plasma pipetted off, so that not more than fifteen minutes elapsed between the withdrawal of the blood and the analysis of the plasma. It is felt that this time is too short to make any appreciable difference in the alkaline content of the plasma. The plasma is then saturated with carbon dioxid at a known tension. One of us (Walker) modified slightly Van Slyke's technic at this point so that the plasma is saturated as follows: A separatory funnel of 250 c.c. capacity is filled from a spirometer with air of a known carbon dioxid percentage. Into this funnel 3 c.c. of the plasma is placed and shaken for two minutes. One c.c. of this saturated plasma is then immediately examined for its carbon dioxid content by the method described by Van Slyke.⁵ The figure obtained after being corrected for temperature and barometric pressure represents the number of milligrams of carbon dioxid in 1 c.c. of plasma. Van Slyke found that multiplying this figure by the constant 35 gives a figure comparable to that obtained for the carbon dioxid tension in the alveolar air.

The air used in saturating the plasma varied in this work in carbon dioxid content from 5.1 to 6 per cent., with an average of 5.8 per cent. in most cases. Comparative studies showed that the final results varied slightly with variations in the carbon dioxid percentage used for saturating the plasma. The amount of variations, however, with these extremes of carbon dioxid percentage was too small to make any practical difference. It seemed, however, that this method for saturating the plasma would be less subject to fluctuations in the carbon dioxid percentage of the saturating air than would be obtained by blowing through the separator, as recommended by Van Slyke. At first the blood determinations were made in duplicate from the same sample, but the results were so consistent that in our later work control determinations were made only when unexpected results were met, and in all cases these were found to agree with the originals.

The observations are grouped by diseases and recorded in tables. Each observation does not represent an individual case, because on a few of the cases more than one study was made. A total of 116 obser-

vations were made on 100 different cases which represented thirty types of disease. As a rule, cases were chosen in which there was not a complication of diseases.

TABLE 1.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN PRIMARY ANEMIA

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3538	39.7	37.7
3690	39.3	40.6
3863	36.7	34.8
4063	42.5	45.5
4064	38.6	40.6
4223	46.2	45.8

In the group of cases of primary anemia shown in Table 1 the carbon dioxid tension in the air varied in different cases by about 10 mm. The relation, however, between the results of the air and the blood studies was very close in each case, and the greatest difference was only 3 points. When a variation did occur, in some cases, the carbon dioxid tension in the air was slightly higher and in others it was slightly lower than that in the blood.

TABLE 2.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN GRAVES' DISEASE

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3434	54.4	43
3591	46	40
3792	43.5	40.2
3748	45.4	45.2
3989	41.2	40
4040	40.9	36.1
4075	40.6	39
4311	43.9	40.6

In the group of cases of Graves' disease represented in Table 2 the carbon dioxid tension in the alveolar air was always slightly higher than that in the blood, and in a few of them this difference was considerable. In the first case with the exceptionally high tension in the alveolar air repeated estimations gave the same result. Just what causes this elevation of the tension in the air in comparison to that in the blood is not clear. It may bear some relation to the fact that the patient's metabolism was about 75 per cent. above normal at this time.

TABLE 3.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN TYPHOID FEVER

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3522	41.8	41.5
3601	32.3	36
3601	38.6	37.5
3601	45.6	42.3

The last two observations in Table 3 were made after the patient was free from fever. In these two cases of this disease the relation between the two tests is close; neither one was consistently elevated above the other.

TABLE 4.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN LUNG ABSCESS

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3834	40.3	41.3
4226	41.2	40.2
4149	41.5	38.8

In the small group of cases of lung abscess represented in Table 4 the results from the two tests correspond very well.

TABLE 5.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN CHRONIC NEPHRITIS

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3507	44	41.5
3520	38.7	37
3369	40.1	36.7
3644	27.9	28
3821	18.2	13.3
3990	39.5	37.8
4253	29.9	32.9

The group of cases summarized in Table 5 is of special interest because it includes some cases of chronic nephritis which showed a marked lowering of the carbon dioxid tension in the alveolar air. The same close relation still exists between the results obtained from the air and the blood studies throughout this group. In some cases the figures for the air tension are slightly higher, in others slightly lower than the figures for the blood.

TABLE 6.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN SYPHILIS

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3857	44.2	44
3857	44.3	43.1
4143	43.2	39.2

The three observations shown in Table 6 made on two cases of syphilis in the stages of a fading general eruption agree closely.

TABLE 7.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN CHRONIC CARDIAC DISEASE

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3539	46.4	38.5
3632	39.1	41.6
3730	43.2	40.9
3460	40.2	38.1
4036	46.3	48.0

The cardiac cases represented in Table 7 were not acutely decompensated at the time, although the patients had to be upright in bed and became dyspneic on slight exertion. Except for the first one in the table, the variation in the results between the blood and air studies is slight. No explanation is offered for this variation. It may be added that this first patient had considerable emphysema.

TABLE 8.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN PNEUMONIA

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3608	37.9	37.1
3630	40.3	34.6
3630	33.8	33.6
3642	34.5	35.7
3677	44.2	47.6
3699	45.9	40.6
3699	47.6	49.0
3825	37.6	37.4
3813	28.5	34.3
3853	37.5	30.5
3883	34.2	30.8
3883	44.7	41
3882	34.7	34.8
3882	41.9	41.6
3885	42	40.3
3944	38.1	41
3965	41.6	42.7
4046	45.1	38.8
4046	45.1	42
4044	33.4	36.1
4053	42.4	38.8
4053	41.5	41.3
4263	36.3	45.5
4263	44	42.3
4280	43.1	38.8
4237	38.8	42

The twenty-six observations on nineteen different cases of pneumonia shown in Table 8 were especially interesting because in the majority of them the respirations were rapid. In many the patients were too ill to cooperate intelligently in the collection of the samples of air. In the cases in which two observations were made, the second was made after the temperature had returned to normal. The group showed variations in the carbon dioxid tension in the alveolar air covering a range of 14 mm.

In the majority of these cases, even in those studied under unfavorable conditions, the results of the blood and air examinations agree very well. In Nos. 3630 and 4263, however, the results from the two tests show a considerable variation, which is also misleading, for in one case the figures for the alveolar carbon dioxid tension are normal, while the blood study suggests an acidosis, while in the other case the reverse is true. No explanation is offered for these variations.

TABLE 9.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD
IN ACUTE ARTICULAR RHEUMATISM

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3715	33.2	35.3
3715	41.0	37.8
3712	37.1	35.7
3712	35.8	36.7
3712	36.6	37
3712	39.8	38.2
3662	35	35.2
3662	31.2	32.5
4088	33.2	37.1
4371	38.2	41
4417	44.5	39.5
4534	43.3	43.7

In the twelve observations on seven cases of acute articular rheumatism represented in Table 9 the comparison between the results is very close although the carbon dioxid tension varied over a range of thirteen points. In some of the cases in which there was a slight difference between the figures for the blood and air, the figure for the air was higher and in others it was lower than that for blood.

TABLE 10.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD
IN DIABETES

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3738	34.7	30.8
3746	36.6	34
3757	34.6	27.6
3880	32.3	31.2
4008	40.8	41.6
3988	35.5	33.6

In five of the six cases of diabetes shown in Table 10 the air and blood show practically the same carbon dioxid tension. The sixth one shows a more marked variation, yet both determinations showed evidence of an acidosis, so that the variation in this case would not be especially misleading. It is interesting to note that in all the cases of this group which showed acidosis the blood was lower in carbon dioxid than the air.

TABLE 11.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD
IN GASTRIC CANCER

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
4336	39.2	38.4
3799	37.4	40.6

In the two cases of gastric cancer represented in Table 11 the results are quite similar.

TABLE 12.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN CIRRHOSIS OF THE LIVER

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
4007	43.7	41.7
4170	38.2	38.1

These two cases of cirrhosis of the liver summarized in Table 12 showed a very close relation between the tests.

TABLE 13.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN ACUTE NEPHRITIS

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3780	27.4	31.2
4160	39.5	40.6
4273	40.3	36.7
4245	46.2	45.5
4314	48.5	48
4380	18.7	15.7

The group of six cases of acute nephritis shown in Table 13 included both mild and severe types, and therefore the variation in carbon dioxid tension in the air varied from above normal to very low. It is interesting to note how closely the air and blood determinations agree in all the cases of this group, in which such marked variations in the carbon dioxid tension occur.

TABLE 14.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN ASTHMA

Number	Carbon Dioxid Tension, Mm.	
	Air	V. Blood
3529	31	37.5
3529	33.6	37
3582	40	37.5
3856	43.3	37.9
3683	40	38.5
3934	39.3	38.5
4161	44.3	42.7
4467	41.8	38.2
4507	37.7	37.8
4563	36	38

Cases 3529 and 4563 in Table 14 were studied during the end of an asthmatic attack and showed the carbon dioxid tension in the air below that in the blood. The figure obtained from the blood examination is presumably the correct one, as difficulty in collecting a proper sample of air during an asthmatic attack has been found by one of us (Walker). In the cases studied between attacks the results from the air and blood determinations agreed very well. Usually the figures for the air estimations were slightly higher than those for the blood.

TABLE 15.—CARBON DIOXID TENSION IN ALVEOLAR AIR AND IN VENOUS BLOOD IN MISCELLANEOUS DISEASES

Number	Diagnosis	Carbon Dioxid Tension, Mm.	
		Air	V. Blood
3559	Tumor rt. kidney	42.2	39.2
3566	Acute endocarditis	41.7	39.5
3787	Acute bronchitis	41.9	39.9
4359	Polycythemia	46.7	46.2
3905	Gonococcus arthritis	39.7	38.5
4254	Tuberculosis	39.7	39.5
3942	Tonsillitis	39.9	36
3955	Perirenal abscess	41.9	40.6
4025	Typhus	45.9	39.2
4031	Erythema nodosum	43.5	41.5
4120	Bronchopneumonia	30	36
4166	Gout	45.9	43.7
4180	Lymphatic leukemia	38.3	43
3281	Portal thrombosis	38.5	37.1
4197	Myxedema and chr. nephritis	38.3	40.2
4299	Addison's disease	38.7	37.1

In the group of sixteen cases shown in Table 15 the carbon dioxid tension in the alveolar air is very similar to the estimated carbon dioxid tension in the venous blood, except in two cases. In each of these cases a difference of six points occurred for which no explanation is available.

In summing up these 116 observations it appears that in the great majority of these cases the carbon dioxid tension in the alveolar air, as collected by the Plesch method, corresponds with that as estimated in the venous blood by Van Slyke's method. Exceptions were met in Graves' disease, pneumonia, and asthma, but even in these diseases, except during an attack of asthma, the variations occurred in only a very small percentage of the cases.

In most of these cases the alveolar air was collected for the first time. In many, especially the febrile cases, the patients were unable to cooperate in the collection of the air sample. It is interesting to note that subsequent studies on several of the cases in which marked differences occurred on the first examination showed practically identical results in the air and blood studies.

From these observations it seems fair to conclude that the carbon dioxid tension in the alveolar air, as determined by the Plesch-Higgins method, agrees very closely with the results obtained by the Van Slyke method of determining the amount of carbon dioxid in the venous blood and is therefore a very accurate index of the amount of carbon dioxid in the venous blood. Furthermore, this method is applicable to a great variety of acute and chronic diseases.

We are indebted to Miss Barker, the laboratory assistant, for estimating the carbon dioxid tension in the samples of alveolar air.

Peter Bent Brigham Hospital.

CHRONIC INFLUENZA IN PULMONARY TUBERCULOSIS *

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It has been our object to obtain data as to the frequency of influenza infection as a complication of phthisis; as to the frequency with which the symptoms of patients diagnosed as having pulmonary tuberculosis, but with negative sputum, may be accounted for by chronic influenza infection, and as to what extent the percentage of recoveries in sanatoriums for tuberculosis have been swelled by the inclusion of cases of influenzal bronchitis.

Influenza bacilli are said to be present in a large percentage of the population.¹ Lockhardt's² summary of the results of Scheller, Holt, Lord, Davis, Allen, Boggs, Grassberger and Wollstein shows that in 172 supposedly normal persons, organisms of the influenza type were found in 25 per cent., while in 427 cases of infection they were found in 50 per cent. Leutscher³ found the influenza bacillus responsible for 22 per cent. of 388 cases of acute infection of the respiratory tract. Hastings and Niles⁴ found influenza bacilli in only 1.5 per cent. of cases of infection of the respiratory tract. Webb⁵ has reported fifteen tuberculous patients who succumbed to epidemic infection with the influenza bacillus. Koch⁶ stated that when influenza is prevalent "cases occur which, to the eye of the clinical observer, exactly resemble incipient tuberculosis, but are not that." Madison⁷ reported six cases of chronic influenzal bronchitis which had much clinical similarity to tuberculosis.

Lord's⁸ work is of special interest. In 1902 he found influenza bacilli present in the sputum of sixty out of 100 patients with cough, presenting themselves at the Massachusetts General Hospital, and with no evidence of tubercle bacilli in the sputum. In 1905 Lord⁹ reported on 186 cases similarly studied. In 59 per cent. of these "organisms having the morphology and staining reactions of influenza bacilli were seen in varying numbers. In 30 per cent. the organisms

* Submitted for publication May 12, 1916.

1. Cabot, R. C.: *Differential Diagnosis*, Ed. 2, 1913, i, 467.

2. Lockhart: *Ann. of Otol., Rhinol. and Laryngol.*, 1914, xxiii, 327.

3. Leutscher: *THE ARCHIVES INT. MED.*, 1915, xvi, 657.

4. Hastings and Niles: *Jour. Exper. Med.*, 1911, xiii, 646.

5. Webb: *Kleb's Tuberculosis*, p. 590.

6. Koch: *British Congress on Tuberculosis*, iii, 94.

7. Madison: *Jour. Am. Med. Assn.*, 1910, lv, 477.

8. Lord: *Boston Med. and Surg. Jour.*, 1902, cxlvii, 659.

9. Lord: *Boston Med. and Surg. Jour.*, 1905, clii, 537.

were shown by culture to conform in all respects to the cause of epidemic influenza." Four of Lord's patients had been admitted to consumptive homes.

The clinical material for this investigation consisted of 320 patients of the Rhode Island State Sanatorium. Two hundred and twenty consecutive patients having negative sputum were examined in the years 1912 to 1915, and 100 patients with positive sputum were examined in the winter and spring of 1916.

The diagnosis of pulmonary tuberculosis in 200 cases having negative sputum was made on the history, symptoms and physical signs. There was a family history of tuberculosis in 36 per cent., a history of pleuritic pain in 55 per cent., of hemoptysis in 45 per cent., of fever in 51 per cent., of night sweats in 46 per cent., and tubercle bacilli were found subsequently in 15 per cent. In thirty-two cases it was thought advisable to test with tuberculin subcutaneously and the result was positive in all. Twenty patients whose sputum was negative for tubercle bacilli and influenza bacilli, cultures having been made for the latter in thirteen cases, were excluded from the above series because the diagnosis of tuberculosis was considered doubtful.

In 50 cases of the first series the cultures were made by Dr. Mary E. Gaffney, all the remaining cultures were made by Dr. Hamblet.

The technic was as follows: The patients were required to deposit in bottles which had been boiled only morning sputum actually raised. In the first 100 cases the technic of Lord was used, with slight variations in the method of washing the particles of sputum selected for inoculation. In the first forty-three cases sterile bouillon or normal salt solution was employed, two washings being made. In the succeeding fifty-seven cases Armstrong's¹⁰ method of washing the sputum in tap water was followed. The culture medium in all three series was agar, the surface of which had been smeared with a few drops of human blood under aseptic precautions. Of the cultures made from the first 100 cases, ninety-three failed to show any influenza-like organisms. Of the seven suspicious cases, three were proved negative to influenza by subcultures, three remained doubtful and in only one was the influenza bacillus positively identified.

In the second series of 100 cases cultures were made only in those cases in which the stained smears from the sputum showed gram-negative rods having some similarity to the influenza bacillus. The technic of Park & Williams¹¹ was followed in this series, the chief

10. Armstrong: *Lancet*. London, 1912. i, 1339.

11. Park and Williams: *Pathogenic Micro-Organisms*, Ed. 4, 1910, p. 358.

point of difference being that the sputum was not washed before inoculating blood agar plates. In accordance with a recommendation from the New York City department of health laboratories, we used in this series agar having a reaction neutral to phenolphthalein. In the other two series the reaction of the agar was acid to phenolphthalein (+1). Cultures were made in twenty cases of the second series, and in six of these micro-organisms having the characteristics of the influenza bacillus were found to be present.

In the third series, for purposes of comparison, a study was made during the spring of 1916 of the sputum in 100 cases which had previously shown tubercle bacilli in the sputum. Sputum for this series was collected in paper sputum cups. Smears stained by the Gram-Weigert method were examined and cultures made by the method of Park and Williams in all suspicious cases. The smears from twenty-three cases showed bacilli having some resemblance to the influenza bacillus. In seven of these the micro-organisms were proved to have the characteristics of the influenza bacillus.

Of the fourteen patients whose sputum contained influenza bacilli, there had been a clinical history of influenza in but three.

The cases in the first two series were examined uniformly at all seasons of the year. Six of the seven sputums from which the influenza bacillus was recovered were examined during the winter and spring months.

From the second and third series of the writers' work it appears that bacilli having the morphological and cultural characteristics of influenza bacilli were recovered from the sputum of 6 per cent. of our sanatorium patients having negative sputum and from 7 per cent. of patients having positive sputum. As these bacilli were never in pure culture or even predominating over other organisms, it does not seem probable that they constituted a serious complication in those having positive sputum or that they were the real cause of lung disease in those having negative sputum. It is perhaps not impossible that a true influenza infection of the lung may have originally been present in some of these cases and that the infection may have so improved that the influenza bacilli ceased to predominate before the patients were admitted to the sanatorium. If it should be granted, however, that all patients in the above series whose sputum was positive for influenza and negative for tubercle bacilli had influenzal bronchitis and were free from active tuberculosis, this would amount to but 6 per cent. of cases having negative sputum and only about 2 per cent. of all patients discharged from the sanatorium. This percentage would be too small sensibly to affect the accuracy of our sanatorium statistics.

SUMMARY

1. Of 100 patients in series 1, diagnosed as having closed tuberculosis whose sputa were cultured for influenza, at least ninety-six were negative.

2. Of 100 patients in Series 2, diagnosed as having closed tuberculosis, influenza bacilli were recovered from six.

3. Of 100 patients in Series 3, with open tuberculosis, influenza bacilli were recovered from seven.

4. Of twenty patients in whom the diagnosis of tuberculosis continued doubtful, the sputum was negative for influenza bacilli in all.

5. In none of the patients examined did the influenza bacilli occur in pure culture nor were they the predominating organism.

CONCLUSION

A study of 320 sanatorium patients, extending over four years, furnished no evidence that influenzal bronchitis frequently simulates or complicates pulmonary tuberculosis.

STUDIES IN BLOOD PRESSURE

WITH ESPECIAL REFERENCE TO DIASTOLIC AND PULSE PRESSURE
READINGS *

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Hypertension is a well-recognized pathologic sign, but the discrimination of varying degrees of high blood pressure is often considered of little value to the diagnostician, and although the diastolic pressure is generally recorded, both it and the pulse pressure are often neglected in making diagnoses and prognoses. The purpose of the present paper has been, therefore, to emphasize especially the valuable data to be obtained from diastolic and pulse pressure readings.

MATERIAL EMPLOYED

The material consists of the hospital records of 305 patients who entered the medical service of the Peter Bent Brigham Hospital during the years 1913, 1914 and 1915. These 305 patients are selected from the first 3,000 admissions to the wards, being all of those who had at least one reading of systolic pressure of 160 mm. of mercury, or more, and in whom at least two tests of the pressure were made. Since it is customary to make two or more tests of the blood pressure in all medical cases showing hypertension or hypotension, and since at least one test is made of every patient admitted, we have here very nearly all the cases of hypertension seen in the medical service during these three years. The Faught mercury manometer instrument was used in this work and the readings were made by the auscultatory method.

All the clinical records in the hospital are made with the greatest care and are frequently checked up. The physical examination of the heart was usually checked up by three or four different physicians, and electrocardiography and Roentgen ray were called into service whenever any doubt existed as to the nature of the cardiac lesion or the presence of enlargement. The diagnosis was verified by necropsy in thirty-one cases. The presence of arteriosclerosis was determined by palpation of the vessel walls (radial and other arteries) and by ophthalmoscopic examination of the retinal vessels.

The maximum and minimum systolic, diastolic and pulse pressure readings were put down and an average taken from these. A few of

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the nephritic cases, in which necropsies were performed, have already been reported by Frothingham.¹

A comparison of the findings in the present study with those of Janeway,² is instructive. The series of cases reported by Janeway consisted of private patients. Only those showing a systolic blood pressure of over 160 mm. of mercury were classified by him as hypertension cases. Of a total of 7,872 patients examined, 11.1 per cent. showed at some time this degree of hypertension, a percentage very similar to that for our hospital patients. He fails to consider diastolic pressure at all. Very few necropsies were performed in this series, no functional renal tests were made, and the electrocardiograph and Roentgen ray were not used.

Of the 305 patients in our series, thirty-two were admitted twice, eighteen three times, four four times and three five times, thus making a total of 397 hospital admissions. A few patients were observed but two or three days, but the great majority remained in the hospital at least one week, and one was under treatment continually for 149 days. Several of the patients were observed from time to time for two years and longer.

The following is a complete list of the data recorded from each case for analysis: hospital number, number of days in the hospital at each visit, initials of name, sex, age, diagnosis, condition of the heart according to physical examination, electrocardiogram, Roentgen-ray examination of chest and postmortem findings; presence or absence of arteriosclerosis, condition of kidneys as suggested by albuminuria (largest amount recorded on any examination), phenolsulphonephthalein test (lowest reading recorded), blood urea nitrogen (highest recorded reading), postmortem findings of the kidney; cerebral symptoms as indicated by palsies, uremia, or convulsions: the Wassermann test; the result at final discharge from hospital. Under blood pressure were recorded the number of readings made, the maximum, the minimum and the average of systolic, diastolic and pulse pressure, together with the percentage heart load as estimated from average readings; the tendency of systolic, diastolic and pulse pressure to rise or fall; the influence of digitalis; time elapsing from first admission to last discharge; subsequent reports of patient's condition after leaving the hospital. These data were obtained from the hospital records and the original observations were made without any reference to utilization in a study of the sort that is here made.

1. Frothingham: *Am. Jour. Med. Sc.*, 1916, cli, 72.

2. Janeway: *THE ARCHIVES INT. MED.*, 1913, xii, 755.

SEX

In our series of patients 163 were male and 142 female. For the year 1914 there were 1,605 males and 1,238 females admitted to the medical and surgical services of the hospital, that is, about 56 per cent. of males and 44 per cent. of females. In our 305 cases 53 per cent. were males and 47 per cent. were females. Since, therefore, more males are admitted to the hospital than females, we may conclude that sex had little bearing in causing hypertension in our cases.

AGE

The Peter Bent Brigham Hospital has no children's ward and very few children are admitted. It will be observed from the table below that the majority of patients were between the ages of 40 and 70 years. In Janeway's² cases 80 or 90 per cent. of the patients were between the ages of 40 and 69 years, and the next largest percentage between 70 and 79 years. As he indicates, these ages are higher than hospital statistics would show. In the present series there were 68.52 per cent. between the ages of 40 and 69 years and the next largest group was found in the period of 30 to 39 years. The following tabulation shows the number of patients and the percentage, by decades as to age:

Age, Years	No.	Per Cent.	Age, Years	No.	Per Cent.
10 to 19.....	11	3.6	50 to 59.....	97	31.8
20 to 29.....	24	7.86	60 to 69.....	56	18.36
30 to 39.....	39	12.78	70 to 79.....	21	6.88
40 to 49.....	56	18.36	81	1	0.32

DIAGNOSES

	No.	Per Cent.
1. Chronic nephritis, with or without myocarditis, but without organic valvular disease.....	141	46.2
2. Chronic nephritis, associated with chronic valvular disease of the heart.....	27	8.9
3. Chronic nephritis, with or without myocarditis, complicated by disease other than of the circulatory system.....	54	17.7
4. Simple chronic myocarditis ³	11	3.6
5. Chronic myocarditis with valvular disease.....	1	0.3
6. Chronic myocarditis with complications other than of circulatory or urinary systems.....	5	1.6
7. Simple valvular disease of the heart, angina pectoris and aortic disease without definite lesions of the kidneys or the myocardium	20	6.6
8. Other conditions	46	15.1

3. Chronic myocarditis is used throughout this paper in the sense of myocardial insufficiency arising from disturbance in the musculature, either functional or organic, in cases not associated with organic valvular lesions. Some of these showed at necropsy fatty degeneration of the myocardium as the only demonstrable lesion of the musculature.

A total of 72.8 per cent. of the patients suffered from chronic nephritis. A differentiation of parenchymatous and interstitial nephritis is not made, for cases that clinically showed all the signs of one variety at necropsy proved often to be the other. These diagnoses were made with considerable care after consideration of all the findings during the patients' stay in the hospital. They were not fixed until the patient was discharged.

Of other conditions, we find that arteriosclerosis was present in 186, or 60.98 per cent. of cases, and absent in 90, or 29 per cent. There were twenty-nine cases in which no record was made, but here the condition if present at all must have been very slight.

In 15.1 per cent. of the patients there was hypertension, without any apparent cardiac or renal disease. The primary conditions in these patients were carcinoma of the lung, prostate and stomach, with more or less metastasis; pulmonary emphysema, cirrhosis of the liver, amyotrophic lateral sclerosis, pernicious anemia, general arteriosclerosis, meningitis, dyspituitarism, cerebral arteriosclerosis, influenza, chronic morphin poisoning, chronic lead poisoning, taenia saginata, hyperthyroidism, syphilis, splachnoptosis, cerebral hemorrhage, constipation, tabes dorsalis, acute gout, hemochromatosis, general miliary tuberculosis, tumor of the cerebellum, varicose ulcers of the leg, chronic malaria with hemorrhoids, mucous colitis and hemorrhoids, obesity, chronic arthritis, and papilloma of the bladder. Of course many of the above conditions were not the cause of hypertension, but their symptoms overshadowed any other obscure disease of the kidney, heart, etc. Undoubtedly there was, in some of these cases, a mild form of chronic nephritis.

A Wassermann test was made in 263 of the cases and in thirty-two, or about 12 per cent., the reaction was positive. Walker and Haller⁴ in their report of routine Wassermann examinations of four thousand hospital patients at the Peter Bent Brigham Hospital found 120 cases of chronic nephritis with hypertension, and only seven of these gave a positive Wassermann reaction (about 5 per cent.), while among ninety-three cases of chronic nephritis without high blood pressure, three had a positive Wassermann reaction. In 1,700 successive medical patients in whom Wassermann reactions were done 12 per cent. had positive reactions, the same percentage as was found in these hypertension cases.

Many of the patients were already in an advanced state of disease when admitted to the hospital wards, and they are not to be compared with early cases of hypertension, such as one sees in private practice.

CASES SHOWING NO ALBUMINURIA

The urine was carefully tested for albumin in every one of the 305 cases reported in this paper, and as a rule an examination was made at least every week or ten days. In thirty-one of our patients no albu-

4. Walker and Haller: Jour. Am. Med. Assn., 1916, lxvi, 488.

min was found, although in eight but one test was made. Of these patients without albuminuria, in seven the high pressure was associated with dilatation of the arch of the aorta, syphilitic aortitis or aortic regurgitation; in five there was angina pectoris, chronic myocarditis or mitral regurgitation; in three there was cirrhosis of the liver with marked arteriosclerosis.⁵ One patient with lead colic improved in symptoms during his eight days in the hospital, the pressure falling to nearly normal. Another patient had amyotrophic lateral sclerosis, associated with arteriosclerosis. There were four cases diagnosed as chronic nephritis, because of the hypertension and a left ventricular hypertrophy, although the urinary findings were negative. All of these cases showed definite arteriosclerosis, however. In one case the diagnosis was general arteriosclerosis.

Of the remaining nine cases without albuminuria four, diagnosed constipation, splanchnoptosis, cancer of the stomach and tabes dorsalis, showed more or less arteriosclerosis. This leaves in this group five patients with no apparent explanation for hypertension. These were chronic morphin poisoning, taenia saginata, general miliary tuberculosis, neurasthenia with tabes dorsalis and chronic malaria. In three of these the heart was slightly enlarged, and the maximum systolic pressure was under 165 in three.

It may be safely stated that albumin can be detected in the great majority of persons suffering from hypertension, if repeated examinations are made. When it is absent, one may look for some cardiovascular disease as the probable cause of the increased tension.

TABLE 1.—PHENOLSULPHONEPHTHALEIN EXCRETION AND SYSTOLIC AND DIASTOLIC PRESSURE

Phenolsulphonephthalein Reading, %	Number Cases	Average Systolic Pressure, Mm.	Average Diastolic Pressure, Mm.
0.....	29	106	117
1 to 10.....	15	104	110
11 to 20.....	25	180	103
21 to 30.....	33	102	112
31 to 40.....	43	185	112
41 to 50.....	40	177	106
51 to 60.....	39	178	77
61 to 70.....	14	169	94
71 to 89.....	6	153	82

5. One of these later proved to have chronic nephritis also.

The phenolsulphonephthalein test of renal function was made in 244 of the 305 patients. In many cases especially those with lower values several tests were made, in which case the minimum reading was selected. The average systolic and diastolic pressures in each case were taken and all averaged together. It is interesting to note the progressive fall in the pressure readings with the rise in the phenolsulphonephthalein readings. Of the thirty-one cases which showed no albuminuria, phenolsulphonephthalein was taken in fifteen. The lowest was 38 per cent. in two. In all the others it was over 40 per cent.

TABLE 2.—THE BLOOD UREA NITROGEN COMPARED WITH THE AVERAGE SYSTOLIC AND DIASTOLIC PRESSURES

Blood Urea N, Mg. per 100 C.c. Blood	Number Cases	Systolic Pressure, Mm.	Diastolic Pressure, Mm.
1 to 20.....	20	187	106
21 to 30.....	14	194	110
31 to 40.....	13	208	115
41 to 60.....	11	186	119
61 to 100.....	10	187	114
101 to 253.....	7	211	132

The blood urea nitrogen was examined in only seventy-five patients. Here again we may observe a gradual tendency to an increase in the average systolic and diastolic pressures. This is especially notable in the diastolic pressure, which shows a more consistent rise than the systolic. This may be due to the other complications influencing the systolic pressure as the intoxication became more profound and interference with cardiac function became more pronounced.

HEART LOAD

W. J. Stone⁶ has contributed an interesting article on the importance of estimating the "heart load" as he calls it. This is determined by dividing the pulse pressure by the diastolic pressure (P.P./D.P.). Now taking 120 mm. as normal for systolic pressure and 80 mm. for diastolic pressure, we have the normal pulse pressure of 40 mm. This makes the normal ratio of pulse pressure to diastolic pressure 50 per cent. Stone finds in normal individuals a variation in heart load between 40 and 60 per cent. If the ratio exceeds this, according to Stone, we have to do with cardiac overload. Barach and Marks⁷ state that according to their findings in normal individuals the pulse pressure equals from 20 to 80 per cent. of the diastolic pressure in 75 per cent. of cases. This wide

6. Stone, W. J.: Jour. Am. Med. Assn., 1913, lxi, 1256.

7. Barach and Marks: THE ARCHIVES INT. MED., 1914, xiii, 648.

variation would tend to vitiate the findings of Stone⁸ in pathologic conditions in which he considers that this ratio is of considerable value in determining the functioning ability of the heart. Stone classifies seventy-five patients with circulatory disturbance into four groups, as follows: (1) hypertension (cerebral group); (2) hypertension (cardiac group); (3) myocardial and valvular lesions with increased heart load ratio; (4) myocardial and valvular lesions with decreased heart load ratio.

These groups he describes as follows: Group 1 showed a systolic pressure of about 202 mm., diastolic of 134 mm., and pulse pressure of 68 mm. The average heart load was 51 per cent.; that is, the heart showed compensatory ability in spite of a high diastolic pressure. In this group are found patients with hypertension, who die of uremia associated with chronic interstitial changes in the kidneys.

In Group 2 there was an average systolic pressure of 180 mm., diastolic pressure of 92 mm. and pulse pressure of 88 mm. The heart load averaged 96 per cent. The distinctive feature in these cases was the low diastolic pressure as contrasted with the high diastolic pressure of the former group. The urine was negative for albumin and casts in a large majority of these cases, and the heart was hypertrophied. There were symptoms of cardiac decompensation.

In Group 3 the systolic pressure averaged 112 mm., the diastolic 60 mm. and the pulse pressure 52 mm. There was a heart load of 86 per cent. In this group were cases of aortic incompetency and other valvular lesions of the heart.

Group 4 was made up of cases showing cardiac dilatation and myocardial incompetence. The systolic pressure averaged 118 mm., the diastolic 92 mm., the pulse pressure 26 mm. and the heart load 28 per cent.

In our series of 305 patients showing a maximum systolic pressure of 160 mm. or over, we have estimated the heart load from the average diastolic and pulse pressure readings and divided them into four groups according to the estimated cardiac load. They are as follows: under 40 per cent., seventeen cases; 40 to 60 per cent., eighty-four cases; 61 to 99 per cent., 159 cases; 100 per cent. and over, forty-five cases.

Heart Load Under 40 Per Cent.—The seventeen cases of this group may be divided into two divisions: typical symptoms of chronic nephritis, 11 cases or 64 per cent.; other cases, 6, or 36 per cent.

The eleven cases of chronic nephritis showed the signs of the interstitial variety in seven and the parenchymatous type in four. The systolic pressures were relatively low, exceeding 200 mm. in only two instances, and averaging 180 mm. The diastolic pressures were high, all over 100 mm., and below 120 mm. in only three. The average was 133 mm. Of the seven patients with symptoms of interstitial nephritis,

8. Stone, W. J.: THE ARCHIVES INT. MED. 1915, xvi, 775.

two showed no signs of cardiac failure, with a heart load of 33 and 38 per cent., respectively. The others showed definite cardiac failure, such as acute dilatation, pulsus alternans and death, dilatation of the heart, auricular flutter and death in uremia, and mitral regurgitation. The four nephritic cases of the parenchymatous type were without any signs of cardiac failure except one case with paroxysmal tachycardia. One patient died of pneumonia and septicemia.

The six cases without chronic nephritis included one with signs of acute nephritis. The heart was negative in two, but in the others there was angina pectoris with cardiac dilatation, displacement of the heart by hydrothorax, mitral regurgitation, and congenital malformation of the heart. The systolic pressures were still lower here, averaging 160 mm., the diastolic pressures averaging 123 mm.

Of these cases with the subnormal cardiac load six died in the hospital or a few weeks after leaving. Two had hemiplegia and one uremia.

Heart Load from 40 to 60 Per Cent.—Stone claims that normally the heart load varies from 40 to 60 per cent. In our hypertension cases there were eighty-four in this group. Seventy-two, or 85 per cent., were cases of chronic nephritis of the interstitial type. In these the heart conditions were as follows: negative, nine cases; hypertrophy without signs of myocardial weakness, forty-three cases; myocarditis without valvular lesions, twelve cases; mitral regurgitation, seven cases; mitral and aortic regurgitation, one case.

There were twelve cases without signs of nephritis. These may be enumerated as follows: meningitis, two; taenia saginata, one; cancer of prostate with metastases, one; general miliary tuberculosis, one; pernicious anemia, one; tabes dorsalis with enlarged heart, one; mucous colitis, one; chronic heart disease, four. Of the heart cases, one was mitral and aortic regurgitation and three were cases of chronic myocarditis.

There were forty-four patients, or more than half, with arteriosclerosis. The diastolic pressure in all the cases averaged from 120 mm. to 140 mm. In only ten cases was it below 100 mm. The average diastolic pressure in the nephritic cases was 122 mm. There were nineteen deaths in this group, uremia occurred in thirteen and cerebral hemorrhages in eight. Of the eighty-four cases, but 28 per cent. gave signs of cardiac decompensation.

Heart Load from 61 to 99 Per Cent.—Under this head are grouped all cases with a moderate overload, less than 100 per cent. Chronic nephritis was present in 118 cases, or 74 per cent., and not present in

forty-one cases, or 26 per cent., making a total of 159 cases. The condition of the heart in the 118 nephritic cases is shown in the following tabulation:

Heart	No.	Heart	No.
Normal	10	Partial or complete block.....	3
Hypertrophied	40	Angina pectoris	3
Dilated	5	Mitral valve disease.....	9
Simple chronic myocarditis.....	15	Aortic valve disease	3
Auricular fibrillation	7	Aortic and mitral valve disease.	2
Premature auricular beats.....	7	Aortic arch dilated	14

Eighty-six of the above cases had more or less arteriosclerosis. There was hemiplegia in seven due apparently to cerebral hemorrhage. Twelve had symptoms of uremia. There were eighteen deaths among nephritic patients as follows: uremia, nine; myocarditis, five; mitral valve disease, one; dilatation of heart, one; cerebral hemorrhage, one; arteriosclerosis, one.

The diagnoses of the 41 nonnephritic cases were as follows:

Diagnosis	No.	Diagnosis	No.
General arteriosclerosis	1	Cardiac hypertrophy ⁹ with com-	
Plumbism	1	plications	3
Pulmonary emphysema	2	Dilatation of heart.....	3
Cerebellar tumor	1	Gout and myocarditis.....	1
Gout and cirrhosis of the liver... 1		Heart block	2
Hyperthyroidism	3	Mitral regurgitation	3
Amyotrophic lateral sclerosis..... 1		Mitral and aortic regurgitation.. 4	
Hemiplegia	2	Aortic regurgitation	1
Chronic morphin poison.....	1	Mitral stenosis	1
Cirrhosis of the liver.....	1	Dilatation of aortic arch.....	1
Chronic myocarditis	8		

The condition of the heart in the forty-one nonnephritic cases was as shown in the following tabulation:

Heart	No.	Heart	No.
Normal	4	Aortic and mitral regurgitation... 4	
Hypertrophied	11	Mitral regurgitation	3
Myocarditis	8	Aortic regurgitation	1
Dilated	5	Mitral stenosis	1
Heart block	2	Aortic arch dilated.....	1
Tachycardia (hyperthyroidism) .. 1			

The deaths that occurred among the forty-one nonnephritic patients were due to the following causes:

Cause of Death	No.
Chronic myocarditis	1
Heart block	1
Acute dilatation of heart.....	1
Hyperthyroidism and tachycardia..... 1	
Meningitis	1
Total	5

9. The term hypertrophy refers to a heart not showing decompensation, as is the case in myocarditis, but with an increased area of cardiac dulness or ventricular hypertrophy, as indicated by the electrocardiograms.

The condition of the heart in the 159 cases of heart overload of from 61 to 99 per cent. was as follows:

Heart	No.	Heart	No.
Normal	14	Heart block (partial or complete)	5
Hypertrophy	51	Tachycardia (hyperthyroidism)	1
Chronic myocarditis	37	Mitral valve disease	13
Dilatation	10	Aortic valve disease	4
Angina pectoris	3	Aortic and mitral valve disease	6
Aortic arch dilated	15		

Thus, not counting the fourteen normal cases and those with a hypertrophied or enlarged heart, where no definite diagnosis of myocarditis or dilatation was made, we find that ninety-four, or 60 per cent., showed definite signs of heart decompensation.

The deaths among the 159 patients with heart overload of from 61 to 99 per cent. were as follows:

Cause of Death	No.	Cause of Death	No.
Uremia	9	Myocarditis	6
Cerebral hemorrhage	1	Dilatation of heart	2
Arteriosclerosis	1	Heart block	1
Meningitis	1	Mitral valve disease	1
Hyperthyroidism and tachycardia	1		

There were 101 cases of arteriosclerosis, and seventeen out of 145 cases in which a Wassermann test was made were positive.

The diastolic pressure averaged much lower than in the two previous groups. In seventy-seven cases, or almost half, it averaged under 100 mm. In most cases it was between 70 mm. and 110 mm. The average diastolic pressure in the ninety-nine nephritis cases was 110 mm.

Heart Load 100 Per Cent and Over.—These cases had a distinct overload, varying from 100 per cent. to a maximum of 220 per cent. The highest three percentages were 220, 173 and 166, all cases of aortic regurgitation. The remaining had an average load between 100 and 161 per cent. Chronic nephritis was present in thirty-two cases, or 71 per cent., while there was no marked nephritis in thirteen cases, or 29 per cent., a total of forty-five cases.

The condition of the heart in the thirty-two nephritic cases is shown in the following tabulation:

Heart	No.	Heart	No.
Normal	3	Complete heart block	2
Hypertrophied	6	Partial block, aortic arch dilated	1
Hypertrophied and bradycardia	1	Arch dilated, heart hypertrophied	4
Dilated	2	Mitral stenosis	1
Simple chronic myocarditis	6	Mitral and aortic regurgitation	1
Myocarditis, dilatation of aortic arch	1	Aortic regurgitation	4

There was some hemiplegia in five of the above cases, due to cerebral hemorrhage, and there were three with symptoms of uremia.

Of the thirteen nonnephritic cases, there were three in which the heart was negative, one of these being a case of lobar pneumonia, one of splachnoptosis, and one of cirrhosis of the liver. There were two cases of hypertrophied heart, one accompanied by cerebral arteriosclerosis, the other by obesity. There were two cases of dilatation of the heart and the aortic arch, two of chronic myocarditis, three of aortic regurgitation, and one of aortic and mitral regurgitation and stenosis.

The condition of the heart in these forty-five cases of overload of 100 per cent. and over is shown in the following tabulation:

Heart	No.
Negative	6
Hypertrophied	9
Chronic myocarditis	9
Dilated	4
Heart block, partial or complete.....	3
Aortic arch dilated.....	4
Mitral stenosis	1
Mitral and aortic valvular disease.....	2
Aortic regurgitation	7
Total	45

Thus we find that thirty, or 66 per cent., of the above cases had definite signs of cardiac decompensation. There were seven deaths among these forty-five patients, with overload of over 100 per cent., the cause being as follows: uremia and heart decompensation, three; cancer and hemiplegia, one; dilated arch and hemiplegia, one; aortic regurgitation and hemiplegia, one; and aortic regurgitation, one.

Thus there were three patients who died of uremia and three with hemiplegia. Three of the patients who did not die also had hemiplegia.

There were thirty-two cases, or 71 per cent., of this group with marked arteriosclerosis. In eight out of forty-three cases with an overload over 100 per cent. in which a Wassermann was taken, the test was positive.

The diastolic pressure averaged over 100 mm. in only six cases. In thirty-nine it was less than 100 mm. and in thirty-three cases it was less than 90 mm.

TABLE 3.—HEART LOAD SUMMARY

Heart Load, per Cent.	Number Cases	Per Cent. with Nephritis	Per Cent. with Normal Hearts	Per Cent. with Hypertrophied Hearts	Per Cent. with Decompensated Hearts	Per Cent. Deaths
Under 40.....	17	64	12	29	59	25
40 to 60.....	84	85	20	52	28	22
61 to 99.....	159	74	8	32	69	14
100 and over.....	45	71	13	19	66	15

ELECTROCARDIOGRAPHIC READINGS

The physical examination of the heart is often obscure in revealing the actual functioning ability of this organ. An electrocardiogram was made in 139 of the patients with hypertension and we have used its readings in making the diagnosis of heart disease. Table 4 is a summary of pressure findings in these cases.

TABLE 4.—BLOOD PRESSURE FINDINGS IN VARIOUS HEART CONDITIONS

Electrocardiogram	Number Cases	Systolic Pressure, Mm.	Diastolic Pressure, Mm.	Pulse Pressure, Mm.	Heart Load, per Cent.
Normal curves	34	171	107	69	71
Left ventricular hypertrophy (uncomplicated)	46	189	111	77	72
Right ventricular hypertrophy (uncomplicated)	4	186	111	72	64
Left ventricular hypertrophy and auricular fibrillation	6	176	98	78	79
Left ventricular hypertrophy, auricular fibrillation and premature ventricular beats	7	175	102	73	71
Left ventricular hypertrophy and premature ventricular beats.....	11	193	113	80	70
Left ventricular hypertrophy and bradycardia	1	205	99	115	116
Left ventricular hypertrophy, auricular flutter and premature ventricular beats	1	156	103	38	36
Left ventricular hypertrophy and paroxysmal tachycardia	1	152	119	40	33
Right ventricular hypertrophy, auricular fibrillation and premature ventricular beats	3	163	109	54	49
Right ventricular hypertrophy and auricular fibrillation	1	135	79	51	64
Complete block	3	199	95	103	110
Complete block and left ventricular hypertrophy	2	184	110	75	75
Delayed conduction or partial block with left ventricular hypertrophy, auricular flutter and ectopic ventricular beats	5	205	119	83	71
Auricular fibrillation, auricular flutter or premature ventricular beats.....	14	167	87	80	91
Total cases	139

There is no very obvious effect on the blood pressure from the various abnormalities revealed by the electrocardiogram. The cases all showed more or less evidence of cardiac decompensation, so that the heart load was generally greater than normal. The pulse pressure,

diastolic pressure and systolic pressure were all moderately high. In the cases of right ventricular hypertrophy the heart load is almost normal, averaging lower than all the other types of abnormality. The cases of complete block are notable for the high pulse pressure associated with increased cardiac load. When complete block was associated with left ventricular hypertrophy this condition was present in only one of the two cases. In partial block the heart load was considerably less. Where there was auricular fibrillation, auricular flutter or premature ventricular beats without ventricular hypertrophy, there was a lowering of both systolic and diastolic readings, while the pulse pressure and the heart load were high; evidence of severe decompensation.

MAXIMUM DIASTOLIC PRESSURE

Many authors agree as to the importance of diastolic readings, but there is little literature in which cases have been studied especially from this point of view. Stone⁶ states that diastolic pressure is a better index of hypertension than the systolic. A sustained pressure of from 100 to 110 signifies hypertension, and it is less influenced by physiologic factors. Warfield¹⁰ believes that the diastolic reading is the most important. A high diastolic reading means constant increased work for the heart and leads to hypertrophy of the left ventricle. A high systolic pressure is invariably associated with a high diastolic pressure, and in failing heart the systolic pressure approaches the diastolic till the pulse pressure becomes nil. He states that it is now generally conceded that high diastolic, high systolic and increased pulse pressure indicate chronic interstitial changes in the kidneys, in the face of normal urinary findings.

In view of the above reference to hypertrophy of the left ventricle, it is interesting to refer to our electrocardiographic findings. Out of the 139 cases the general average of diastolic readings was considerably above normal, even in those without evidence of a predominant left ventricle. There were, however, 57 per cent. in which the electrocardiogram showed left ventricular hypertrophy.

Stone also emphasizes the importance of the diastolic pressure, which represents the constant pressure between systoles. He believes that it is a better index of peripheral resistance and of hypertension than the systolic pressure. A sustained diastolic pressure of from 105 mm. to 110 mm. or above signifies hypertension, irrespective of the height of the systolic pressure, and the diastolic is less influenced by physiologic factors than the systolic pressure. Janeway,¹¹ on the other hand, has declared that except in cases of aortic regurgitation, marked

10. Warfield: *New York Med. Jour.*, 1915, cii, 509.

11. Janeway: *Am. Jour. Med. Sc.*, 1906, cxxxi, 772.

bradycardia and the senile pulse, when the diastolic pressure must be determined before hypertension can be diagnosed, the diastolic pressure is not of very great value. In 305 cases with systolic pressure of 160 mm. or over the diastolic pressure was as shown in the following tabulation:

Maximum Diastolic Pressure, Mm.	No. Cases	Maximum Diastolic Pressure, Mm.	No. Cases
51 to 60.....	1	131 to 140.....	37
61 to 70.....	5	141 to 150.....	30
71 to 80.....	5	151 to 160.....	17
81 to 90.....	22	161 to 170.....	11
91 to 100.....	34	171 to 180.....	3
101 to 110.....	50	181 to 190.....	2
111 to 120.....	50	191 to 200.....	2
121 to 130.....	35	205	1

Thus, in 305 cases with a maximum systolic pressure of 160 mm. or over, 32 per cent. showed a diastolic pressure of from 101 mm. to 120 mm., while the readings gradually shaded off to 60 mm. as the minimum and 205 mm. as the maximum. Many cases, however, did fall to a lower diastolic pressure than 60 mm. during their stay in the hospital.

Maximum Diastolic Pressure of 60 mm.—The diastolic in this one case fell as low as 40 mm. There was a high pulse pressure, caused by syphilitic aortitis, with aortic regurgitation and a slight glomerular nephritis, as proved by necropsy.

Maximum Diastolic Pressure from 61 to 70 mm.—This subnormal reading occurred in five cases, in four of which there was marked aortic regurgitation, while in the fifth there was marked arteriosclerosis and dilatation of the aortic arch. Nephritis was not present at all, or there was merely a mild secondary involvement of the kidneys.

Maximum Diastolic Pressure from 71 to 80 mm.—The five cases in this class were aortic regurgitation with a mild secondary nephritis, a case of myocarditis with chronic bronchitis, cirrhosis of the liver, diabetes mellitus and one mild case of chronic nephritis, in which the phenolsulphonephthalein rose from a minimum of 32 per cent. to 57 per cent.

Maximum Diastolic Pressure from 81 to 90 mm.—Though these readings are above the normal of 80 mm., yet for a systolic pressure of 160 mm. or over they are relatively low. Sixteen of these cases gave no signs of any marked nephritis. The phenolsulphonephthalein test was made in a few and ranged from 50 to 70 per cent. The majority showed an enlargement of the heart, and there were two cases of aortic regurgitation. There were six cases of nephritis. The low diastolic reading may be explained in all of these, however. Two patients were

in a late stage of the disease and died a few days after admission. In one the primary condition was diabetes mellitus and the nephritis was but a mild one as indicated by a phenolsulphonephthalein reading of 63 per cent. The fourth case was one of hyperthyroidism, with marked cardiac decompensation and auricular fibrillation. In the fifth case the low diastolic pressure was accounted for by the evidence of a dilated aortic arch. Finally, there was one case with chronic interstitial nephritis, with a phenolsulphonephthalein output of 28 per cent. and 34 mg. of blood urea nitrogen in 100 c.c. of blood, but in this case there was complete heart block and a bradycardia of 30 to 40 beats.

Maximum Diastolic Pressure from 91 to 100 mm.—Of the thirty-four cases in this group showing a moderate diastolic hypertension, there were fourteen without nephritis and twenty with it. In the non-nephritic cases the phenolsulphonephthalein test, taken in most of them, gave readings of from 52 to 89 per cent. In two there was aortic regurgitation with some involvement of the mitral valve; in others there were other cardiac lesions, a case of emphysema and tumor of the brain. In a few the hypertension was not explained.

In an advanced form of chronic interstitial nephritis one would expect a high diastolic reading. There were five of these, as indicated by a phenolsulphonephthalein reading of from 0 to 20 per cent. Four of these patients died in the hospital and one had auricular fibrillation. Cardiac decompensation was present in all of these. In seven the phenolsulphonephthalein was moderately low, from 20 to 40 per cent. The low diastolic reading was explained in two of these by the presence of aortic regurgitation, in three by a chronic myocarditis with auricular fibrillation. In one there was a cerebral hemorrhage, and in one there was nephritis without signs of decompensation. The remaining cases of nephritis were mild with phenolsulphonephthalein of over 40 per cent.

Thus, in those with only a moderately high diastolic pressure nephritis is frequently observed, but one may expect to find only a mild grade, as indicated by the phenolsulphonephthalein test, or else very advanced disease with broken cardiac decompensation.

Maximum Diastolic Pressure from 101 to 120 mm.—Of the 100 cases in this group, fifty-six were diagnosed as chronic nephritis. In the 44 per cent., however, in which a diagnosis of nephritis was not made, the hypertension was no doubt due to changes in the kidneys, this condition being overlooked by the dominance of other pathologic processes. Thus, in half of these nonnephritic cases a phenolsulphonephthalein test was made, and in ten the reading was between 22 and 50 per cent. In the remainder the hypertension may be explained wholly or in part by such conditions as advanced arteriosclerosis, myo-

carditis, alcoholism, chronic lead poisoning, mitral valvular disease, angina pectoris, hyperthyroidism, cerebral hemorrhage, and cirrhosis of the liver.

Most of the fifty-six renal cases in this group showed a fairly advanced stage of renal interstitial processes, as indicated by the phenolsulphonephthalein output. This was as follows:

No. Cases	Phenolsulphone- phthalein, %
3.....	No record
4.....	0
7.....	1 to 19
24.....	20 to 40
18.....	40 to 61

There were five cases of lead poisoning in this group, but only three, or 3 per cent. of the group, showed aortic regurgitation.

Maximum Diastolic Reading from 121 to 150 mm.—Of the 102 patients included in this group, only ten, or about 9 per cent., were not diagnosed as having chronic nephritis, but in four of these the phenolsulphonephthalein read from 10 to 50 per cent., so that there was some impairment of kidney function. The remaining six cases were generalized arteriosclerosis, aneurysm with aortic regurgitation, chronic myocarditis, syphilis with enlarged liver and spleen, renal calculus with mitral regurgitation, and arteriosclerosis with dilated aortic arch.

About 91 per cent. of the patients gave very definite signs of chronic nephritis, with albuminuria, hypertrophy of the heart and uremia. In eighty-seven of these cases the phenolsulphonephthalein read as follows:

No. Cases	Phenolsulphone- phthalein, %
17.....	0
7.....	1 to 10
18.....	11 to 30
17.....	31 to 40
13.....	41 to 50
15.....	51 to 62

Among the nephritic cases there were two cases of aortic regurgitation, making three altogether, with a diastolic pressure between 121 and 150 mm.

Maximum Diastolic Pressure from 151 to 170 mm.—Among the twenty-eight cases in this group there was but one without definite signs of nephritis. The diagnosis in the case of this patient was tabes dorsalis. There was no albuminuria, the heart was normal, but arteriosclerosis was present. The hypertension in this patient may be explained in part at least by severe gastric crises.

The remaining twenty-seven patients had definite signs of chronic nephritis, with hypertrophy of the heart. There was one with a phenolsulphonephthalein output of 60 per cent., and this patient had syphilitic

aortitis. There were two cases of hemiplegia, an additional one with a cerebral hemorrhage. The phenolsulphonephthalein test was performed in twenty-five of the cases. In the two in which this test was not performed the blood urea nitrogen was 79 mg. and 181 mg., respectively. There was no case of aortic regurgitation. The results of the test in these twenty-five cases are as follows:

No. Cases	Phenolsulphone- phthalein, %
4.....	0
2.....	1 to 10
4.....	11 to 20
10.....	21 to 40
4.....	41 to 50
1.....	60

Maximum Diastolic Pressure from 171 to 200 mm.—Seven cases fell in this group, all of which were cases of chronic nephritis, as confirmed by necropsy in three. A phenolsulphonephthalein test was made in all. There was no excretion from one; 1 to 10 per cent. in three; from 11 to 20 per cent. in two, and 23 per cent. in one. There was fatty degeneration of the heart in two of the necropsied cases and the retromanubrial dulness was increased in two. Arteriosclerosis was present in all.

Maximum Diastolic Pressure 205 mm.—There was but one case with so high a maximal diastolic pressure. The systolic pressure in this case was 240 mm. There was chronic nephritis with a phenolsulphonephthalein of 48 per cent., complicated by a hemiplegia involving the left leg and arm.

TABLE 5.—COMPARISON OF MAXIMUM DIASTOLIC WITH SYSTOLIC PRESSURE

Maximum Diastolic Pressure, Mm.	Average of Maximum Systolic Pressure, Mm.	Number Cases	Per Cent. Cases Nephritis	Aortic Regurgitation, Number Cases
60	190	1	0	1
61 to 70	(160-170)	5	0	4
71 to 80	173 (160-185)	5	20	1
81 to 90	180 (160-250)	22	27	2
91 to 100	184 (160-250)	34	53	4
101 to 120	190 (160-260)	100	56	3
121 to 150	215 (163-230)	102	91	5
151 to 170	205 (180-250)	23	95	0
171 to 200	262 (230-300)	7	100	0
205	240	1	100	0

Table 5 indicates the progressive increase in the percentage of chronic nephritis in proportion to the rise in diastolic pressure. By averaging the corresponding maximum systolic pressures we note a less regular rise in the systolic pressures. The pressure of 160 mm. appears several times in the groups in which 20, 27, 58 and 56 per cent. of the cases are chronic nephritis. While of course a high systolic pressure suggests the presence of chronic nephritis, a diastolic pressure of 120 mm. and over is very strong evidence of the presence of this condition, and one may expect more than half the cases to show evidence of chronic Bright's disease if the diastolic pressure reaches from 90 to 120 mm. A subnormal diastolic pressure, or one below 80 mm., is rarely associated with a chronic nephritis.

VARIATIONS IN PRESSURE DURING TREATMENT

Norris¹² states that rest causes a decrease in systolic, diastolic and pulse pressure. All of the patients in our series were put to bed for a few days at least. In general, the first systolic pressure taken was very high. Patients who remained in the hospital had numerous records taken and these were charted. In some cases the reading was made daily or every two days. It thus was very easy in most cases to tell at a glance the tendency of systolic, diastolic and pulse pressure to increase or decrease. Most cases showed a definite tendency up or down, but in some there was a distinct rise after a progressive fall, to be followed again by a fall. These cases we have classed with certain cases in which there was little if any variation. Hecht¹³ has shown the marked effect of sanatorium and hospital treatment in reducing the pressure, which again becomes elevated on resuming natural life conditions. This was repeatedly verified in patients who returned for a second, third or fourth visit to the hospital. In our statistics several factors came into play in causing variations in the pressure. Above all, rest with a restricted diet tended to lower hypertension. A few cases were definitely influenced by digitalis, but as a rule this influence was only temporary and therefore not considered in our table. Nitrites were seldom given and their effect was fleeting. Most of the patients who died showed a progressive fall in systolic and diastolic pressure during the last weeks of life. The following tabulation shows the variations in 304 cases:

	No. Cases with Tendency to Rise	No. Cases with Tendency to Fall	No. Cases Fluctu- ating or Maintained
Systolic pressure	40	190	74
Diastolic pressure	43	181	80
Pulse pressure	71	151	82

12. Norris: Blood Pressure, Its Clinical Applications, Philadelphia, Lea & Febiger, 1914.

13. Hecht: Ztschr. f. klin. Med., 1912, lxxvi, 87.

We see from the above table that there is a marked tendency for the systolic pressure to fall or remain high; the diastolic pressure is also most likely to fall, but it is more likely than the systolic to remain stationary or rise, while pulse pressure generally falls, but is more likely to rise or remain unchanged than the other two. The greatest fluctuations were usually to be found in systolic readings, and the least in pulse pressure. In some cases, however, the greatest changes were observed between the maximum and minimum pulse pressure or diastolic pressure.

DIGITALIS AS AFFECTING PRESSURE

In hypertension cases digitalis is of distinct value when decompensation of the myocardium has set in. Theoretically, as Norris¹² says, digitalis should increase tension, especially in hypotension cases. Clinically, however, it is often found to lower the pressure, and is of especial value in failing heart, in which case it may lower tension by increasing the elimination of urine or by decreasing venous stasis.

In our cases digitalis was used to restore broken heart compensation. If only a few doses were given the effect was naturally only transient. There were sixty-nine patients, however, in whom digitalis seemed to have a definite influence on the pressure curves, as proved by a careful comparison of the dates when digitalis was started and stopped with the blood pressure chart. In these sixty-nine cases the heart and circulatory system showed the following conditions:

Conditions Found	No. Cases		
Myocarditis and decompensation.....	22		
Chronic nephritis and cardiac decompensation.....	31		
Chronic nephritis without cardiac disease.....	9		
Angina pectoris	5		
Arteriosclerosis	1		
Hyperthyroidism	1		

	No. of Cases Tendency to Rise	No. of Cases No Change	No. of Cases Tendency to Fall
Systolic pressure	43	6	20
Diastolic pressure	23	12	32
Pulse pressure	44	15	10

In fourteen cases there was a progressive rise in systolic, diastolic and pulse pressure. In five they all fell synchronously.

It was a common occurrence to note, following the administration of digitalis, a marked increase in the systolic and pulse pressure, the latter often being largely caused by the fall in diastolic pressure. The rise in systolic pressure caused an improvement in symptoms and the general condition of the patient.

DEATHS

According to Norris¹² a systolic pressure of 180 mm. is not often exceeded without symptoms, and constant pressures of 200 mm. or over are generally not long maintained before leading to some catastrophe, such as angina pectoris, uremia or apoplexy.

Janeway² analyses the deaths of 212 of his private patients who at some time prior to death had a systolic pressure above 160 mm. Of these, 32.6 per cent. died "a gradual cardiac death," while in his cerebral group there were 40.8 per cent. The majority of deaths occurred between the age 40 and 60 years. He also says that a systolic pressure above 200 mm., other things being equal, constitutes a certain presumption in favor of death by uremia or apoplexy. Finally, he concludes as follows:

Death in this type of cardiovascular disease, among patients in private practice, occurs in the followings ways, arranged in the order of their frequency: First, by gradual cardiac insufficiency; second, with uremic symptoms; third, by apoplexy; fourth, from some complicating acute infection; fifth, in an attack of angina pectoris; sixth, from purely accidental and unrelated causes; seventh, in a paroxysm of acute edema of the lungs; eight, after the manner of cachexia.

In our series, fifty-two deaths occurred while the patients were under treatment in the hospital, or a few days after their discharge. Other patients died at their homes or in other institutions, but the exact facts attending their final illness being uncertain, they are not included in our list.

Of the fifty-two cases, a postmortem was performed in thirty-one. In twenty-one this was not possible, but every other means available was made use of to determine the nature of the disease. Eight patients were under observation for less than one week. The remainder were watched for periods varying from eight days to two years. The age of these fifty-two patients at the time of death is shown in the following tabulation.

Age, Years	No. Cases	Per Cent.
70 to 76.....	3	5.7
61 to 69.....	9	17.3
40 to 60.....	26	50.0
30 to 39.....	7	13.3
20 to 29.....	4	8.0
16 to 19.....	3	5.7

The greatest number of deaths occurred between the ages 40 and 60 years, and the next most commonly between the ages 61 and 69 years. The next period in point of frequency was the period from 30 to 39 years. The youngest person who died was 16 and the oldest 76 years.

The dominant pathologic conditions as diagnosed before death or proved by necropsy are shown in the following tabulation:

Conditions Found	No. Cases
Chronic nephritis	16
Chronic nephritis and myocarditis	16
Chronic nephritis and pulmonary tuberculosis	1
Chronic nephritis and intestinal obstruction	1
Chronic nephritis and lobar pneumonia	1
Chronic nephritis and aortic insufficiency	2
Chronic myocarditis	5
Chronic myocarditis and angina pectoris.....	1
Heart block	1
Endocarditis of mitral, tricuspid and aortic valve....	1
Carcinoma of lung.....	1
General carcinomatosis, metastases.....	3
Syphilitic (?) meningitis.....	1
Hemorrhagic meningo-encephalitis	1
General miliary tuberculosis.....	1

There were therefore thirty-seven cases in which there was marked chronic nephritis, usually of the interstitial variety, and ten cases in which there was serious derangement of the circulatory system. In seven, any cardiorenal lesions that existed were of such a secondary nature as to cause no comment in the record of the patient. The apparent cause of death in these fifty-two cases is shown in the following tabulation:

Apparent Cause	No. Cases	Apparent Cause	No. Cases
Uremia	24	Anginal attack	1
Heart failure	11	Venous thrombosis	1
Terminal apoplexy	5	Miliary tuberculosis	1
Acute cardiac dilatation.....	3	Pregnancy	1
Obstruction to bronchus (cancer). 2		Pneumonia and septicemia.....	1
Meningitis	2		

The above patients were very carefully observed during the last days of life, so that the data, often confirmed by necropsy, are as accurate as it is possible to make them. Twenty-nine patients, or about 55 per cent., died with cerebral symptoms, uremia or apoplexy. Fifteen, or about 28 per cent., died with progressively or suddenly impaired heart function, following some preexisting cardiac lesion. Two died of respiratory failure due to mechanical obstruction. The two cases of meningitis might be included with the cerebral group. In one, pregnancy proved to be the last straw in a patient with chronic myocarditis and nephritis.

Systolic Pressure in Fatal Cases.—Twenty-eight, or about 53 per cent. of the patients who died, gave a maximum systolic pressure of 200 mm. or over. Most of these died with uremic symptoms, only three of those dying having given a systolic reading less than 200 mm. The other patients with a maximum pressure of less than 200 suffered from cardiac disease, tuberculosis, meningitis, cancer, etc.

Diastolic Pressure in Fatal Cases.—Forty-five, or about 86 per cent., had a diastolic pressure of 100 mm. or above. These included most of the patients with chronic nephritis who died of uremia. There were seven whose diastolic pressure never reached 100 mm. One died of carcinoma; two of endocarditis of the aortic valve; two of myocarditis with thromboses; one of uremia from chronic interstitial nephritis; and one of meningitis. The variations in blood pressure in the fifty-one patients who died is shown as follows:

	Systolic Pressure	Diastolic Pressure	Pulse Pressure
Rose	11	9	15
Maintained about same.....	16	17	15
Fell	24	25	21

The variations in these patients are not strikingly different from the variations that generally occur in patients with hypertension who do not die. Of course the readings just ante mortem are not counted here, but the tendency of the pressure to rise or fall during the patients' stay in the hospital. The tendency of the systolic, diastolic and pulse pressure was certainly less towards a fall than it was in the whole group of cases taken together.

CONCLUSIONS

1. In the wards of a general hospital hypertension occurs almost as frequently in females as in males.

2. About 68 per cent. of cases of hypertension are found in patients between 40 and 69 years of age, the greatest number occurring between the ages 50 and 59 years.

3. Almost three fourths of the cases, 72.8 per cent., had definite signs of chronic nephritis. Arteriosclerosis was also common. The next most common conditions were circulatory disturbances, chronic myocarditis or valvular lesions.

4. If several specimens of urine are examined, albumin is usually to be found at some time in cases of hypertension. If it is persistently absent, the cause of the high blood pressure is generally vascular or cardiac disease, and not renal.

5. The readings of the phenolsulphonephthalein test vary inversely with the average systolic and diastolic readings, this ratio being especially noticeable in the case of diastolic readings.

6. The blood urea nitrogen varies directly with the average systolic and diastolic readings.

7. In hypertension cases with a normal heart load of 40 to 60 per cent., 85 per cent. had chronic nephritis. Of those cases in which the load was under 40 or over 60 per cent., only about 70 per cent. were cases of nephritis. When the load was under 40 per cent., the

prognosis proved to be most unfavorable, but there were several cases without signs of cardiac decompensation. Among those whose heart load was 40 to 60 per cent., only 28 per cent. gave signs of cardiac decompensation; of those whose heart load was 61 to 99 per cent., there were 59 per cent. with cardiac decompensation, and of those whose load was 100 per cent. or more, 66 per cent. showed signs of cardiac decompensation. Hypertrophy of the heart without decompensation was most common in cases with a normal load; when the load was 100 per cent. or over, there were the fewest cases of heart hypertrophy without decompensation and the greater number of decompensated hearts.

8. Subnormal diastolic pressures suggest the presence of aortic regurgitation and the absence of chronic nephritis. With the rise in diastolic pressure the incidence of aortic regurgitation rapidly decreased and the percentage of nephritis steadily increased, much more consistently than when the systolic pressure alone was examined.

9. During the hospital treatment there was usually a decrease in the systolic, diastolic and pulse pressures, but this was more frequent with the systolic than the diastolic or pulse pressure. The pressures may rise or remain about the same.

10. In cardiac decompensation the effect of digitalis was rather to increase pulse pressure and systolic pressure and cause a fall in the diastolic pressure.

11. Deaths in hypertension patients most frequently occurred between the ages of 40 and 60 years, and the underlying condition was either chronic nephritis or chronic disease of the heart, or a combination of the two. More than half the deaths occurred with symptoms of uremia or apoplexy. Twenty-eight per cent. died with signs of progressive heart failure. The patients in more than half the fatal cases had had a systolic pressure of over 200 mm., and 86 per cent. had had diastolic pressure of over 100 mm.

I desire to express my appreciation to Dr. Henry A. Christian, Physician-in-Chief of the Peter Bent Brigham Hospital, under whose direction this work was undertaken, and to Dr. Francis W. Peabody for their valuable suggestions.

THE SUBSEQUENT HISTORY OF PELLAGRINS IN SPARTANBURG COUNTY, S. C., WHO SURVIVED THE INITIAL ATTACK*

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INTRODUCTION

In a preceding paper of this series¹ we have discussed the initial attacks of pellagra in 1,180 cases in Spartanburg County in relation to race, sex and age. The death rate in the year of initial attack for these cases was 15.8 per cent. In the present paper we purpose to consider those patients in this same series who survived the year of initial attack, more particularly in regard to their freedom from recurrences in subsequent years, the appearance of such recurrences, the death rate in recurrent attacks and the relation of these phenomena to the duration of the disease. In a subsequent paper we purpose to discuss their relation to race, sex, age, complicating disorders, diet and medicinal treatment. It is hoped that definite criteria may thus be afforded for prognosis in pellagra, for this particular geographical district at any rate. So far as we are aware there are in the literature no reported observations on a large series of noninstitutional pellagrins followed over a period of years, although there are reports of successful treatment of rather large series of cases in a single year and of institutional pellagra during a series of years.

RECURRENT ATTACKS APPEARING IN EACH YEAR

The total number of recurrent attacks of pellagra (with erythema) recorded as occurring in each year in the pellagrins of this series is shown in Table 1, together with the total incident attacks recorded in each year, for comparison. The recorded recurrences have increased

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* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* This paper has been written since Dr. Garrison and Dr. Siler were recalled to active duty in the Medical Corps, U. S. Navy, and the Medical Corps, U. S. Army, respectively. Although they are quite familiar with the general nature of the paper, they are not personally responsible for the detailed compilation of data or for the specific deductions drawn from them.

1. Siler, Garrison and MacNeal: The Incidence of Pellagra in Spartanburg County, S. C., and the Relation of the Initial Attack to Race, Sex and Age. THE ARCHIVES INT. MED., 1916 (in press).

progressively every year, and although the data in regard to recurrences in 1914 are undoubtedly less complete than for 1912 and 1913, nevertheless the highest number of recorded recurrences, namely, 250, was in 1914. This adds confirmation to our conclusion, based on the study of the incident cases, that pellagra has been steadily and progressively increasing in Spartanburg County since 1908. It is interesting to note that the number of pellagrins with recurrence of the disease is nearly equal to the number with initial attacks, not in the same year, but in the preceding year, in each instance. In fact, the agreement is remarkably close in the years since 1909. In that year there were fifty-seven recorded initial attacks and in 1910 there were fifty-eight pellagrins with recurrences. In 1910 there were 141 initial attacks and in 1911 there were 141 recurrences. In 1911 there were 234 initial attacks, followed by 230 recurrences in 1912. In 1912 there were 211 initial attacks and in 1913 there were 238 pellagrins who had recurrences. In 1913 the initial attacks numbered 251 and in 1914 the pellagrins with recorded recurrences numbered 250. This agreement would seem to be more than accidental, and it suggests that the individuals newly attacked in one year make up a very important part of the persons showing recurrences in the following year. We shall subsequently have opportunity to inquire into this relationship in more detail.

TABLE 1.—DISTRIBUTION OF PELLAGRINS WHO HAD RECURRENT ATTACKS OF PELLAGRA IN SPARTANBURG COUNTY ACCORDING TO YEAR OF RECURRENCE AND OF INCIDENT PELLAGRINS ACCORDING TO YEAR OF ONSET

Year	Before 1908	1908	1909	1910	1911	1912	1913	1914	Totals
Recurrent pellagrins.....	80	22	34	58	141	230	238	250	1,053
Incident pellagrins.....	57	20	57	141	234	211	251	209	1,180

For the purpose of a comparative study the record of each pellagrins after the year of initial attack has been tabulated for each year under one of the four following headings:

1. Recurrent attack, which indicates the presence of the diagnostic erythema during the respective year.

2. Living without recurrence, which indicates that the patient was free from definite symptoms of pellagra during the respective year.

3. Dying without recurrence, which indicates that the patient died after January 31 of the respective year without definite signs of a recurrent attack.

4. Uncertain, which indicates that the patient passed from observation or gave vague and indefinite evidence of a recurrent attack.

To complete the tabulation it was necessary also to include the instances of death during recurrent attack, as these patients would, of course, be without record in subsequent years. In every instance a death occurring in January has been credited to the preceding year.

The record of the fifty-seven pellagrins incident previous to 1908 is difficult to present in tabular form, and part of these cases will therefore be considered briefly according to the year of onset.

In 1888 Pellagrin 1263, a white man, aged 44, suffered his first attack. He had a recurrence in 1889 and died in that year.

In 1892 Pellagrin 20, a white man, aged 62, had his first attack of pellagra. When seen by us in 1912 he stated that he had had a recurrent attack every year since 1892. He had a definite attack of pellagra in 1912 and died Feb. 27, 1913, without a recurrence of the erythema in that year.

In 1893 Pellagrin 533, a white woman, aged 41, suffered her first attack of pellagra. She had recurrence in 1894 and again in 1895, with recovery. Subsequently she remained well until 1913, when she again suffered a very typical attack of pellagra and was seen by us. She was a very intelligent woman of the moderately well-to-do class, and was quite certain that the manifestations present in 1913 were identical with those she had observed twenty years before. The physician who attended her in the previous attack was also consulted by us. He did not remember any signs of pellagra, but thinks that he may well have overlooked them at that time, as his attention was directed especially to other pathologic conditions in the patient. This woman recovered from the attack in 1913 and remained free from recurrence in 1914 and 1915.

In 1894 Pellagrin 1086, a white girl, aged 15, had her first attack of pellagra. She died in 1889, the assigned cause of death being cancer of the tongue. The history of recurrent attacks of pellagra is indefinite and uncertain. Pellagrin 805, a white woman, aged 31, died of pellagra during her first attack in 1894.

In 1898 Pellagrin 1223, a white man, aged 54, suffered his initial attack of pellagra. The disease recurred each year to 1908, in which year he committed suicide by drowning.

In 1900 Pellagrin 1187, a white man, aged 33, developed pellagra. He had recurrences each year to and including 1906. In 1907 and 1908 the evidence of recurrence is uncertain. The disease recurred definitely in 1909 and each year until death during a recurrent attack in 1911. In 1900 also, Pellagrin 633, a white man, aged 48, suffered his first attack, with recurrence in 1901 and 1902. From 1903 to 1909, inclusive, a period of seven years, there was no recurrence. The eruption reappeared each year in 1910, 1911 and 1912. In 1913 and 1914 there was no recurrence. This patient was an inmate of the Columbia

State Hospital for the Insane in 1912 and part of 1913. In 1914, when seen by us, he seemed quite clear in his mind. Pellagrin 352, a white woman, aged 23, developed pellagra in 1900 and had recurrent attacks in 1901, 1902 and 1903, with death at the Columbia State Hospital for the Insane in 1903.

In 1901 there were also three recorded initial attacks. Pellagrin 354, a white girl, aged 16, developed pellagra in that year and suffered recurrent attacks each year to the end of 1909. She died Feb. 7, 1910, without erythema. Pellagrin 1272, a white man, aged 40, died of pellagra in May, 1901, apparently during the initial attack. Pellagrin 876, a colored woman, aged 53, also died in an initial attack of pellagra in 1901.

In 1902 two new cases were recognized. Pellagrin 426, a white woman, aged 24, died in an initial attack in this year. Pellagrin 1223, a white man, aged 56, developed the disease in 1902 and had recurrences each year to 1906, inclusive, dying in 1906.

All these fourteen patients with onset previous to 1903 furnished, therefore, forty-eight instances of recurrence, seventeen instances of a year without recurrence and five instances of uncertain record up to 1907, inclusive. Of the fourteen patients, eight died before 1908, four in the year of onset, three during the year of recurrence and one during the year without recurrence.

In 1903 there were recorded six incident cases; in 1904 there were five. There were ten in 1905, six in 1906 and fourteen in 1907. In two cases incident before 1908 it was not possible to ascertain the year of origin. These were both colored women, Pellagrins 1260 and 1261, and were said to have died in the initial attack of pellagra at the ages of 16 and 36 years, respectively, some time previous to 1908. The subsequent fate up to 1914 of the forty-one cases incident from 1903 to 1907, inclusive, is shown in detail in Figures 2, 3 and 4, and their behavior up to 1908 is summarized in Table 2. This group of 41 cases furnished fifty-three instances of recurrence, three instances of non-recurrence and twenty-four instances of uncertain record during the years 1904 to 1908, inclusive. Of the forty-one patients, seven died in the initial attack, four died in the year of recurrence and one died in a year in which there was no recurrence. There remained twenty-nine of the forty-one patients alive at the end of 1908. Up to the end of 1907 these forty-one patients furnished seven instances of death in initial attack, thirty-two instances of recurrence, three deaths in recurrence, two instances of survival of a year without recurrence, one instance of death during a year without recurrence and sixteen instances of year without definite record. Adding to these figures the analogous data for the fourteen patients with onset previous to 1903 and the two patients with onset in unknown years, we get a result which

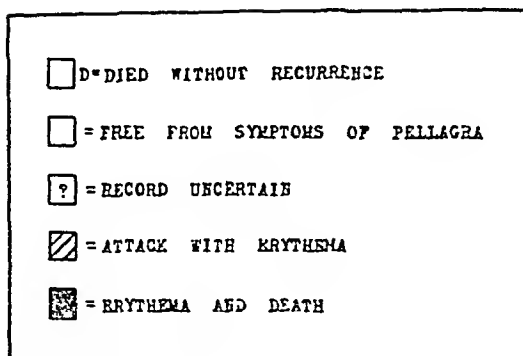


Fig. 1.—This key indicates the manner in which the behavior of each pellagrins is designated in the subsequent figures.

TABLE 2.—SUBSEQUENT HISTORY UP TO 1908 OF THE FORTY-ONE PELLAGRINS WITH ONSET FROM 1903 TO 1907, INCLUSIVE

	1903	1904	1905	1906	1907	1908	Totals
Initial attacks	6	5	10	6	14	..	41
Death in year of onset.....	2	0	0	2	3	..	7
Pellagrins with recurrence.....	..	2	6	11	13	21	53
Death in year of recurrence.....	..	0	1	1	1	1	4
Pellagrins living without recurrence.....	..	0	0	1	1	1	3
Pellagrins dying without recurrence.....	..	0	0	1	0	0	1
Pellagrins without definite record.....	..	2	3	5	6	8	24
Pellagrins alive at end of year.....	4	9	18	20	30	29	..
Pellagrins considered in year.....	6	9	19	24	34	30	..

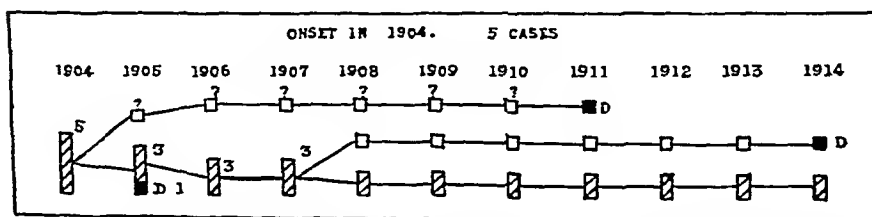
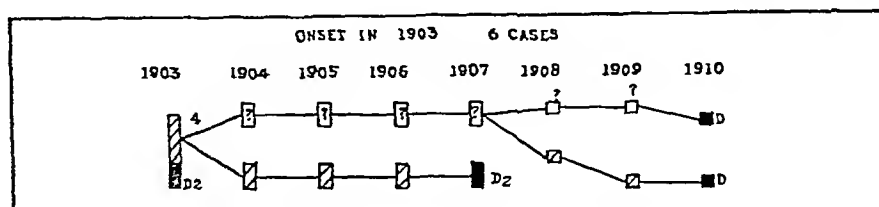


Fig. 2.—Behavior during subsequent years of pellagrins with onset in 1903 and 1904. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

shows fifty-seven pellagrins with onset before 1908, furnishing thirteen instances of death in year of onset, eighty instances of recurrence, seven deaths in a year of recurrence, nineteen instances of survival of a year without recurrence, two deaths in a year in which there was no recurrence and twenty-one instances of a year without definite record. At the end of 1907 there remained alive thirty-five of the fifty-seven patients with onset previous to 1908, and of these there were six who contracted pellagra previous to 1903, eighteen with onset from 1903 to 1906, inclusive, and eleven with onset in 1907.

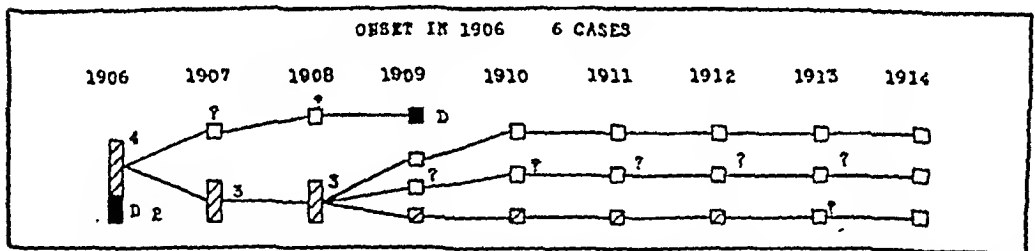
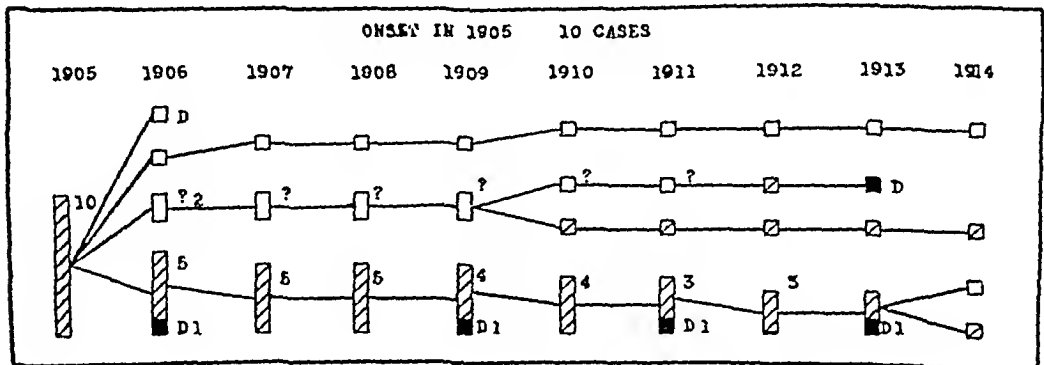


Fig. 3.—Behavior during subsequent years of pellagrins with onset in 1905 and 1906. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

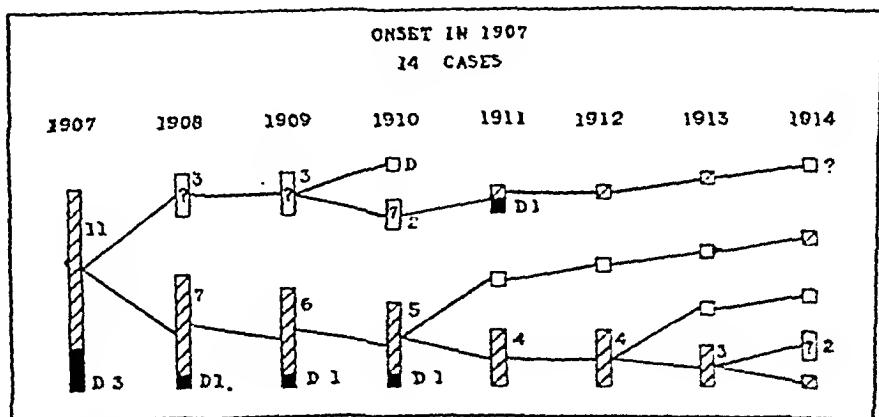


Fig. 4.—Behavior during subsequent years of pellagrins with onset in 1907. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

The fate of these thirty-five survivors during the period 1907 to 1914 is summarized in Table 3.

The table shows a distinct tendency for the number of recurrences to diminish in the later years, while the relative proportion of those who escape without recurrence tends to increase. Thus, in 1908 there were twenty-two with recurrence and four who escaped, a ratio of $5\frac{1}{2}$ to 1. In 1912 this ratio became 3 to 1; in 1913 it was 2 to 1 and in 1914 it became 1 to 1. The ratio of recurrences to escapes from recurrence for all years was 193 to 55, or approximately $3\frac{1}{2}$ to 1 for this group of cases. It is probable that those pellagrins who acquired the disease in these early years and then recovered would be less likely to appear in our records than would those who showed numerous recurrences, and therefore we are inclined to consider this ratio as somewhat too large rather than too small. The indicated death rate

TABLE 3.—SUBSEQUENT HISTORY UP TO 1914 OF THE THIRTY-FIVE PELLAGRINS WITH ONSET PREVIOUS TO 1908 WHO REMAINED ALIVE FEB. 1, 1908

	Before 1908, Total	1908	1909	1910	1911	1912	1913	1914	Totals
Pellagrins with recurrence.....	80	22	20	19	18	15	12	7	193
Deaths in year of recurrence.....	7	2	3	3	4	0	2	1	22
Pellagrins living without recurrence	19	4	5	4	5	5	6	7	55
Pellagrins dying without recurrence	2	0	0	2	0	0	1	0	5
Pellagrins without definite record...	21	9	8	5	2	1	2	4	52
Pellagrins alive at end of the year..	35	33	30	25	21	21	18	17
Pellagrins considered in the year....	44	35	33	30	25	21	21	18

in recurrence for this whole group of cases was twenty-two in 193, or 11.4 per cent. This figure is probably too low rather than too high, because some of these early fatal cases were doubtless recorded as deaths in initial attack, when, as a matter of fact, there had been an unrecognized attack in a previous year. The indicated death rate in initial attack for the fifty-seven pellagrins incident before 1908 was 22.8 per cent. and, as was pointed out in the preceding paper of this series, we regarded this figure as too high for this same reason. This criticism does not apply, however, to the events subsequent to 1907 in this group, and even here the deaths have been fifteen in a total of 113 recurrences, or 13.1 per cent. Certainly, this would indicate that pellagra is not a disease of progressive degeneration presenting a more unfavorable prognosis the longer it has existed in the patient, but rather that the danger to life in a recurrence is not significantly different from

the danger in the initial attack and may, perhaps, be somewhat less. It will be interesting to see how these suggestions are borne out in the larger and more accurately recorded groups of cases which had their onsets in years subsequent to 1907.

In 1908 there were twenty recorded incident pellagrins, of whom two died in the year of onset. The subsequent behavior of the eighteen survivors is shown in detail in Figure 5, and is summarized in Table 4. In this group of cases the ratio of pellagrins with recurrence to pellagrins without recurrence also shows a diminution in the later years. Thus, in 1909 the ratio was 7 to 1; in 1912 it was 3 to 1, and in 1914 less than 2 to 1. The deaths in recurrent attack for this group were only four in fifty-nine recurrent attacks, a death rate of 6.8 per cent., again somewhat lower than the death rate in initial attack for the same group, namely, 10 per cent.

TABLE 4.—SUBSEQUENT HISTORY UP TO 1914 OF THE EIGHTEEN PELLAGRINS WHO SURVIVED AN INITIAL ATTACK OF PELLAGRA IN 1908

	1909	1910	1911	1912	1913	1914	Total
Pellagrins with recurrence.....	14	10	11	9	8	7	59
Deaths in year of recurrence.....	2	0	2	0	0	0	4
Pellagrins living without recurrence.....	2	4	3	3	4	4	20
Pellagrins dying without recurrence.....	0	1	0	0	0	0	1
Pellagrins without definite record.....	2	1	1	1	1	2	8
Pellagrins alive at end of the year.....	16	15	13	13	13	13	..
Pellagrins considered in the year.....	18	16	15	13	13	13	..

In 1909 there were fifty-seven recorded incident cases of pellagra with sixteen deaths in the year of initial attack, a rate of 28.1 per cent. The subsequent fate of the forty-one survivors is shown in detail in Figure 6 and is summarized in Table 5. In the following five years there were in this group eighty-four recurrences, a year with one recurrence or with several recurrences being counted as a unit recurrence. There were fourteen deaths in recurrence, the indicated death rate being 16.7 per cent., again less than the death rate in initial attack for the same group. In 1913 and 1914 there were no deaths recorded in this group. The ratio of pellagrins with recurrence to pellagrins who escaped recurrence also shows a progressive diminution in the later years. This ratio was nearly 5 to 1 in 1910; exactly 4 to 1 in 1911; a little more than 2 to 1 in 1912; less than 1 to 1 in 1913 and a little more than 1 to 2 in 1914.

In 1910 there were 141 recorded incident cases of pellagra with twenty-eight deaths in the year of initial attack. The indicated death rate in the year of onset was, therefore, 19.9 per cent. The subsequent

fate of the 113 survivors is shown in detail in Figure 7 and is summarized in Table 6. In this group of pellagrins there were during the four years from 1911 to 1914, 214 recurrences with thirty-one deaths during the year of recurrent attack, a mortality rate of 14.5 per cent. in recurrent attack. The mortality in recurrent attack seems to have diminished progressively in the later years. Of the eighty-eight pellagrins of this group with recurrence in 1911, no less than sixteen died, a mortality of 18.2 per cent. The mortality in 1912 was 15 per cent.; in 1913 it was 12.2 per cent. and in 1914 it was 4 per cent., again suggesting that prognosis as to life in a given attack of pellagra is better the longer the patient has suffered from the disease. The ratio between pellagrins with recurrence and pellagrins who escaped recurrence in each year shows also in this group a progressive diminution in the later years, from about 5 to 1 in 1911 to 2 to 1 in 1912, 1.3 to 1 in 1913 and 0.76 to 1 in 1914.

TABLE 5.—SUBSEQUENT HISTORY UP TO 1914 OF THE FORTY-ONE PELLAGRINS WHO SURVIVED AN INITIAL ATTACK OF PELLAGRA IN 1909

	1910	1911	1912	1913	1914	Totals
Pellagrins with recurrence.....	29	24	16	8	7	84
Deaths in year of recurrence.....	4	7	3	0	0	14
Pellagrins living without recurrence.....	6	6	7	10	13	42
Pellagrins dying without recurrence.....	2	1	0	0	0	3
Pellagrins without definite record.....	4	4	4	6	4	22
Pellagrins alive at end of the year.....	35	27	24	24	24	..
Pellagrins considered in the year.....	41	35	27	24	24	..

TABLE 6.—SUBSEQUENT HISTORY UP TO 1914 OF THE 113 PELLAGRINS WHO SURVIVED AN INITIAL ATTACK OF PELLAGRA IN 1910

	1911	1912	1913	1914	Totals
Pellagrins with recurrence.....	88	60	41	25	214
Deaths in year of recurrence.....	16	9	5	1	31
Pellagrins living without recurrence.....	17	26	31	33	107
Pellagrins dying without recurrence.....	3	1	2	1	7
Pellagrins without definite record.....	5	7	10	18	40
Pellagrins alive at end of the year.....	94	84	77	75	...
Pellagrins considered in the year	113	94	84	77	...

In 1911 there were 234 recorded incident attacks of pellagra with thirty-three deaths in the year of initial attack. The indicated mortality in the year of onset was therefore 14.1 per cent. The subsequent fate of the 201 survivors in this group is shown in detail in Figure 8 and is summarized in Table 7. In this group of pellagrins there occurred in the three years 258 recurrences with thirty-seven deaths, the indicated death rate in year of a recurrence being, therefore, 14.3 per cent., slightly higher than the mortality during year of onset in this group. Of the 130 pellagrins with recurrence in 1912, there were twenty-one who died during that recurrence, giving a death rate of 16.2 per cent. In 1913 the death rate in recurrence in this group fell to 12 per cent. and in 1914 it was 13.2 per cent. The ratio of pellagrins with recurrence to pellagrins who escaped recurrence during the year again shows a progressive diminution with the lapse of time, being about 2.5 to 1 in 1912, approximately 1 to 1 in 1913 and 0.65 to 1 in 1914.

In 1912 there were 211 recorded incident pellagrins with twenty-seven deaths in initial attack, giving a death rate of 12.8 per cent. in the year of onset; and in 1913 there were 252 recorded incident pellagrins with thirty-eight deaths in the year of onset, giving a death rate in the year of first attack of 15.1 per cent. The subsequent observations on the 184 survivors of the initial attack in 1912 and on the 214 survivors of the initial attack in 1913 are shown in detail in Figure 9 and are summarized in Table 8. Of the 184 survivors of initial attack in 1912, there were ninety-four with recurrence in 1913 and fifty-six with recurrence in 1914. The sum of these recurrences is 150, with 18 deaths, 12 per cent., almost the same as the death rate in the initial attack of the same group. Of the ninety-four recurrences in 1913, death occurred in twelve, or 12.8 per cent., and there were six deaths in the fifty-six recurrences in 1914, or 10.7 per cent. The ratio of pellagrins with recurrence to pellagrins living without recurrence was about 1.5 to 1 in 1913 and approximately 0.9 to 1 in 1914. The 1914 recurrences observed in the 214 survivors with onset in 1913 numbered ninety-five, with four deaths, or 4.2 per cent. The ratio of pellagrins with recurrence to pellagrins without recurrence was very nearly 1.5 to 1. The sum total of all these instances of observations in years subsequent to that of the initial attack is shown in Table 9.

Leaving out the 315 instances of uncertain record and the thirty-five instances of death without recurrence, we have 1,670 instances in which definite information is available concerning a pellagrin in a year subsequent to recovery from the initial attack. In 1,053 of these 1,670 instances, or 63.1 per cent., the record shows recurrence of the disease during the year, and in 617 instances, or 36.9 per cent., there was free-

dom from recurrence. For the whole pellagrous population of Spartanburg County, after recovery from the initial attack, the chance of freedom from recurrence in a given subsequent year was a little better than 1 in 3.

In the 1,053 recurrent attacks there occurred 130 deaths. The general death rate in recurrences was therefore 12.3 per cent., somewhat lower than the general death rate in year of initial attack.

TABLE 7.—SUBSEQUENT HISTORY UP TO 1914 OF THE 201 PELLAGRINS WHO SURVIVED AN INITIAL ATTACK OF PELLAGRA IN 1911

	1912	1913	1914	Totals
Pellagrins with recurrence.....	130	75	53	258
Deaths in year of recurrence.....	21	9	7	37
Pellagrins living without recurrence.....	51	73	82	206
Pellagrins dying without recurrence.....	2	3	1	6
Pellagrins without definite record.....	18	27	30	75
Pellagrins alive at end of the year.....	178	166	158	...
Pellagrins considered in the year.....	201	178	166	...

TABLE 8.—SUBSEQUENT HISTORY UP TO 1914 OF THE 184 PELLAGRINS WHO SURVIVED AN INITIAL ATTACK IN 1912 AND OF THE 214 WHO SURVIVED AN INITIAL ATTACK IN 1913

	Incident in 1912			Incident in 1913
	1913	1914	Totals	1914
Pellagrins with recurrence.....	91	56	150	95
Deaths in year of recurrence.....	12	6	18	4
Pellagrins living without recurrence.....	60	65	125	62
Pellagrins dying without recurrence.....	6	2	8	5
Pellagrins without definite record.....	24	43	67	51
Pellagrins alive at end of the year.....	166	158	...	203
Pellagrins considered in the year.....	184	166	...	214

THE FATE OF SURVIVING PELLAGRINS AS INFLUENCED BY THE DURATION OF THE DISEASE

In the preceding examination of the subsequent history of pellagrins incident in each year it has appeared that recurrence was more common in the second year of the disease and that the tendency to recurrence diminished in the later years. There has also seemed to be an indication of a lower death rate in the later years. It therefore appears

to be worth while to rearrange the data in such a way as to make clearer the nature of these relationships.

The behavior in the second year of all those who survived the year of onset is summarized in Table 10 for each annual group of new cases after 1907, and those with onset before 1908 are considered as a single group. Of the 814 pellagrins with onset before 1914 who survived the year of initial attack, there are 114 for whom the record in the second year of the disease is indefinite or uncertain and nineteen who died in the second year without recurrence of the erythema. There remain 681 patients, of whom 482, or 70.8 per cent., showed a recurrent attack in the year following the onset, and 199, or 29.2 per cent., survived the second year without recurrence of pellagra. In this series of

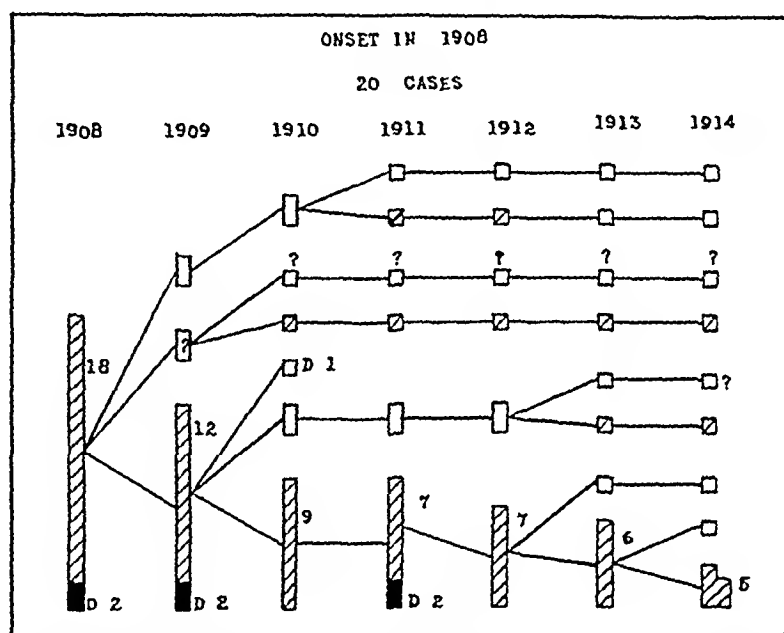


Fig. 5.—Behavior during subsequent years of pellagrins with onset in 1908. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

pellagrins, therefore, there were approximately three in every ten survivors of the initial attack who escaped recurrence in the next year. The proportion of pellagrins with recurrence in the second year is higher than for the average of all years subsequent to the year of onset, for which the rate, as has been shown, was 63.1 per cent. Of the 482 pellagrins with recurrence in the second year of the disease, sixty-three died during that year, the death rate in the first recurrence, that is, in the second year of the disease, being, therefore, 13.1 per cent., somewhat lower than the death rate in year of onset for the whole 1,180 pellagrins, namely, 15.8 per cent., and lower than the death rate in year of onset for the 971 pellagrins incident previous to 1914, namely, 16.2 per cent. (971 cases, 157 deaths), but slightly higher than the gen-

eral death rate for all recurrences, which, as has been shown, was 12.3 per cent.

Of the 482 pellagrins with recurrence in the second year, there were 419 who survived it. Of these 419, there were ninety-one with first recurrence in 1914, so that further records are not available for them. The behavior of the other 328 during the third year of the disease is

TABLE 9.—SUMMARY OF BEHAVIOR IN SUBSEQUENT YEARS OF THE 824 PELLAGRINS WHO SURVIVED AN INITIAL ATTACK PREVIOUS TO 1914

	Year of Inelidenee							
	Before 1908, Totals	1908	1909	1910	1911	1912	1913	Totals
With recurrence.....	193	59	84	214	258	150	95	1,053
Deaths in recurrence.....	22	4	14	31	37	18	4	130
Living without recurrence.....	55	20	42	107	206	125	62	617
Dying without recurrence.....	5	1	3	7	6	8	5	35
Without definite record.....	52	8	22	40	75	67	51	315
Total case-years in the group.....	305	88	151	368	545	350	213	2,020

TABLE 10.—BEHAVIOR DURING THE SECOND YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED THE FIRST YEAR

Year of Onset	Survivors	Reurrences in Second Year	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908.....	44	32	4	1	1	10
1908	18	14	2	2	0	2
1909	41	29	4	6	2	4
1910	113	88	16	17	2	5
1911	201*	130	21	51	2	18*
1912	184	94	12	60	6	24
1913	213	95	4	62	5	51
Totals	814*	482	63	199	19	114*

* Including one white child, sex unknown.

summarized in Table 11. Of these 328 pellagrins, 228 had a recurrence again in the third year, twenty-nine with fatal termination; sixty-four survived the third year without recurrence, seven died without recurrence, and for twenty-nine of the cases the record is uncertain as regards recurrence. After subtracting the twenty-nine with indefinite record and the seven who died without recurrence, there remain 292

with definite record in regard to recurrence in the third year. Of these, 228, or 78.1 per cent., suffered a recurrence in the third year and sixty-three, or 21.9 per cent., lived through the third year without recurrence. This indicates that those who recover from a recurrence in the second year of the disease are somewhat more liable to recurrence the next year than are those who are just recovering from their initial attack. Of the 228 pellagrins with consecutive attacks to the third year of the disease, twenty-nine died in recurrence in this third year, a mortality rate in the second consecutive recurrence amounting to 12.7 per cent., which is slightly lower than the mortality in recurrent attacks of the second year discussed above.

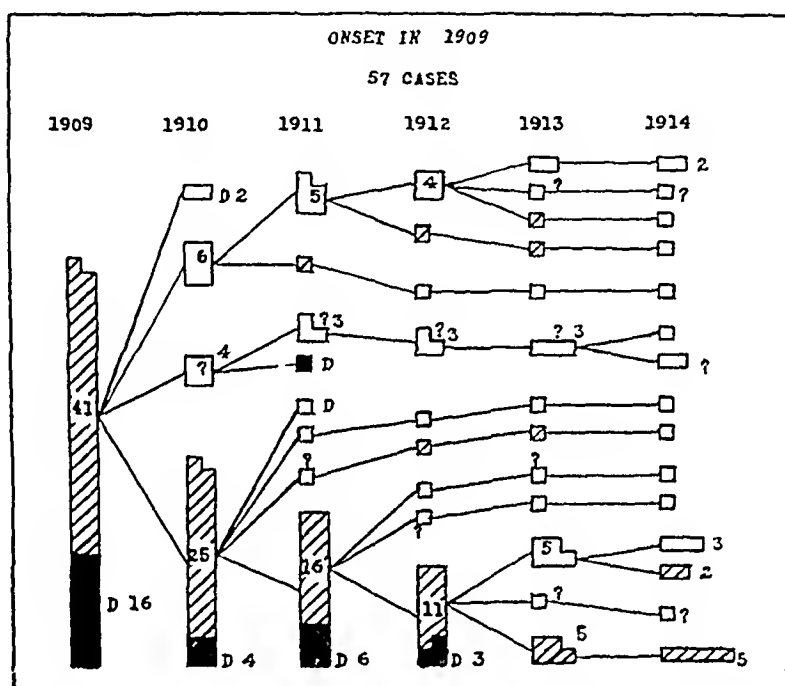


Fig. 6.—Behavior during subsequent years of pellagrins with onset in 1909. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

Of the 199 pellagrins who escaped recurrence during the second year (Table 10), sixty-two had their onset in 1913 and notes for the third year are not available for these. The behavior of the other 137 of this group is summarized in Table 12. Of these 137 pellagrins who escaped recurrence in the second year, fifteen are without definite record for their third year. There remain 122 whose behavior in the third year is definitely recorded. Of these, sixteen suffered a recurrence in the third year, 13.1 per cent. of the 122. The other 106, or 86.9 per cent., escaped recurrence in the third year. Of the sixteen who had a recurrent attack, one died, 6.3 per cent. These figures indicate that absence of recurrent attack in the second year of the disease has not guaranteed freedom from recurrence the following year, but

that, nevertheless, the chance of recurrence in the third year has been very much reduced for this group as compared with those pellagrins with recurrence in the second year (Table 11). In that group a recurrent attack appeared in 78.1 per cent., and only 21.9 per cent. escaped in the third year, while in this group 86.9 per cent. escaped in the third year.

TABLE 11.—BEHAVIOR DURING THE THIRD YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED A RECURRENCE IN THE SECOND YEAR

Year of Onset	Survivors of Recurrence in Second Year	Behavior in Third Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	28	28	1	0	0	0
1908	12	9	0	2	1	0
1909	25	22	6	1	1	1
1910	72	56	8	12	1	3
1911	100	66	8	29	3	11
1912	82	47	6	20	1	14
Totals	328	228	29	64	7	+29

TABLE 12.—BEHAVIOR DURING THE THIRD YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED THE SECOND YEAR WITHOUT A RECURRENCE

Year of Onset	Survivors of Second Year without Recurrence	Behavior in Third Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	1	0	0	1	0	0
1908	2	0	0	2	0	0
1909	6	1	0	5	0	0
1910	17	3	1	14	0	0
1911	51	6	0	41	0	4
1912	60	6	0	43	0	11
Totals	137	16	1	106	0	15

In the second year there were 114 pellagrins without definite record, of whom fifty-seven had their initial attack in 1913 and are therefore without any available record for the third year. The behavior during the third year of the remaining sixty-three is summarized in Table 13. The figures of this table have little significance except to show that

a year of indefinite symptoms was sometimes followed by a frank recurrence and sometimes by a year of good health. Most of the patients in this group continued to have uncertain records, because they could not be seen personally and the information obtained seemed to us too unreliable to warrant a definite decision concerning recurrence or its absence.

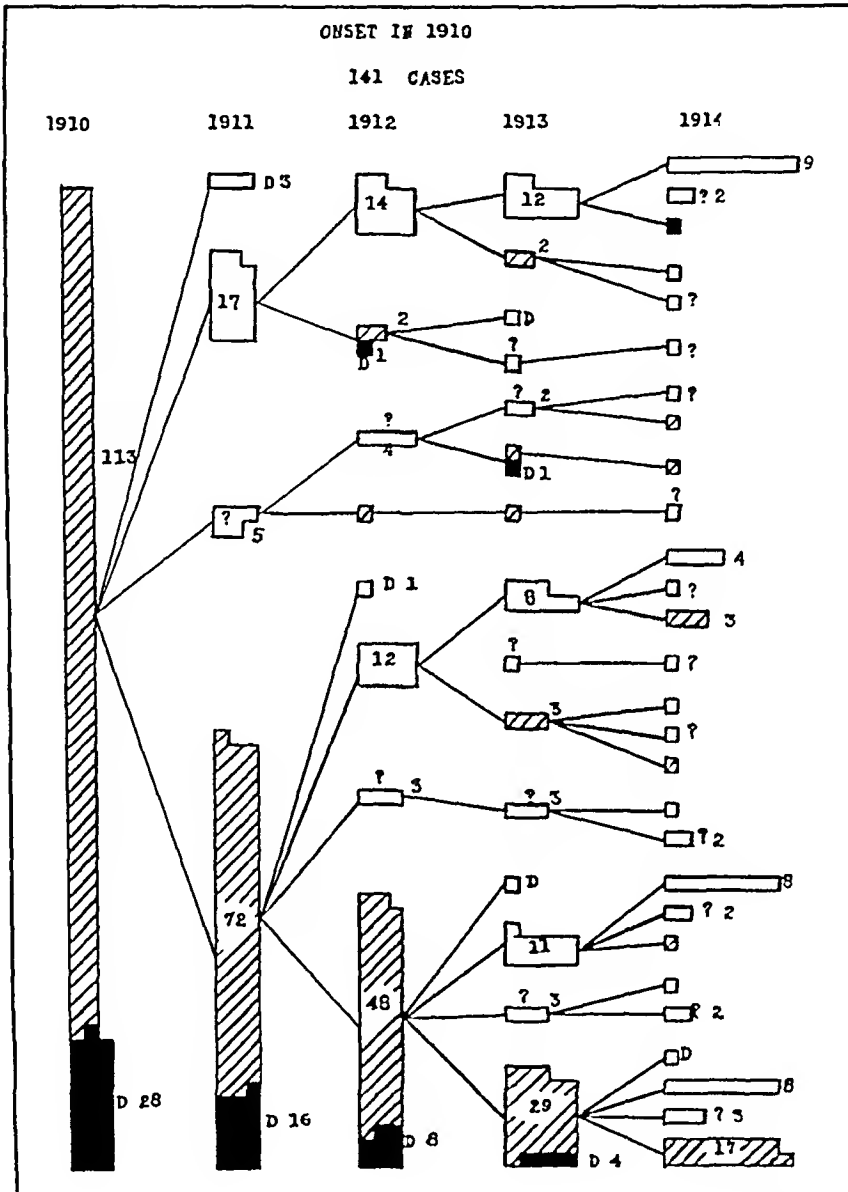


Fig. 7.—Behavior during subsequent years of pellagrins with onset in 1910. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

When we come to a consideration of the events of the fourth year of the disease on this same plan, we are confronted with the necessity of considering nine distinct groups of survivors of the third year, namely, (1) those who had recurrence in the second year and also recurrence in the third year; (2) those with recurrence in the second

year, but no recurrence in the third year; (3) those with recurrence in the second year and an indefinite record in the third year; (4) those without recurrence in the second year and with recurrence in the third year; (5) those without recurrence in the second year and without recurrence in the third year; (6) those without recurrence in the second

TABLE 13.—BEHAVIOR DURING THE THIRD YEAR OF THE DISEASE OF THOSE PELLAGRINS WITHOUT DEFINITE RECORD IN THE SECOND YEAR

Year of Onset	Pellagrins without Definite Record in Second Year	Behavior in the Third Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1903 ..	10	0	0	0	0	10
1903	2	1	0	0	0	1
1909	4	1	1	0	0	3
1910	5	1	0	0	0	4
1911	18*	3	1	3	0	12*
1912	24	3	0	2	1	18
Totals	63*	9	2	5	1	48*

* Including one white child, sex unknown.

TABLE 14.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED RECURRENT ATTACKS IN THE SECOND AND THIRD YEARS

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1903	27	23	2	3	0	1
1903	9	9	2	0	0	0
1909	16	14	3	1	0	1
1910	48	33	4	11	1	3
1911	58	35	4	16	1	6
Totals	158	114	15	31	2	11

year and without definite record in the third year; (7) those without definite record in the second year and with recurrence in the third year; (8) those without definite record in the second year and free from recurrence in the third year; (9) those without definite record in the second year and without definite record in the third year. Only the

groups numbered (1), (2), (4) and (5), above, seem to be of sufficient value to warrant their separate consideration. We shall consider each of them separately and group together into one table all the remaining cases which have an indefinite record in either the second or third year or both. All of the patients to be considered in the fourth year had their first attack in the year 1911 or before.

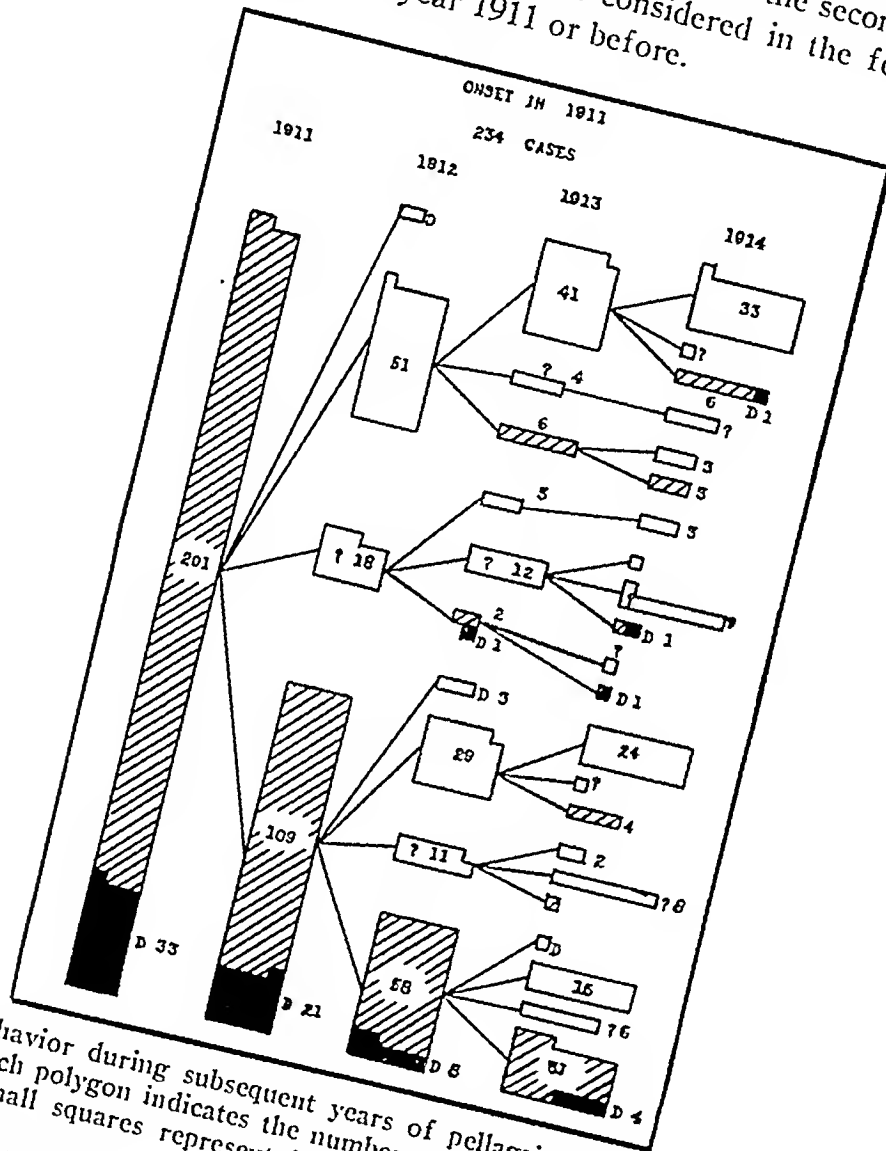


Fig. 8.—Behavior during subsequent years of pellagrins with onset in 1911. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

As has been shown in Table 11, there were 228 pellagrins with recurrence in both the second and the third year of the disease. Of these, twenty-nine died in the third year, leaving 199 survivors. After subtracting the forty-one with onset in 1912, there remain 158 patients in this group for consideration in the fourth year of pellagra. Their behavior in this year is shown in summarized form in Table 14. Of the 158 patients, 114 had recurrence of pellagra in the fourth year, fifteen of these dying; thirty-one escaped recurrence; two died without recurrence and for eleven the record is indefinite. After subtracting

the two who died without recurrence and the eleven with uncertain record, there remain 145 cases for consideration in respect to recurrence. Of these, 114 had recurrence, 78.6 per cent., and thirty-one, or 21.4 per cent., escaped recurrence. The deaths in the fourth consecutive annual attack numbered fifteen in 114 pellagrins who suffered this

TABLE 15.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO HAD RECURRENCE IN THE SECOND YEAR AND SURVIVED WITHOUT RECURRENCE IN THE THIRD YEAR

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	0	0	0	0	0	0
1908	2	0	0	2	0	0
1909	1	0	0	1	0	0
1910	12	3	0	8	0	1
1911	29	4	0	24	0	1
Totals	44	7	0	35	0	2

TABLE 16.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO ESCAPED RECURRENCE IN THE SECOND YEAR AND SURVIVED A RECURRENCE IN THE THIRD YEAR

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	0	0	0	0	0	0
1908	0	0	0	0	0	0
1909	1	0	0	1	0	0
1910	2	0	0	0	1	1
1911	6	3	0	3	0	0
Totals	9	3	0	4	1	1

attack, the indicated mortality rate being 13.2 per cent. higher than has been observed in the recurrences in earlier years of the disease. However, these cases all arose previous to 1912, which fact may require consideration before making too strict comparisons.

As shown in Table 11, there were sixty-three pellagrins who had a recurrence of pellagra in the second year and survived without recur-

rence in the third year. Of these, nineteen had their first attack in 1912 and cannot be considered during the fourth year of their disease. The behavior of the remaining forty-four during the fourth year is summarized in Table 15. Of these forty-four pellagrins two are without definite record in the fourth year. Of the other forty-two, there were seven, or 16.7 per cent., with recurrence of the disease and thirty-five, or 83.3 per cent., without recurrence in the fourth year. There were no deaths from pellagra in this entire group during the fourth year.

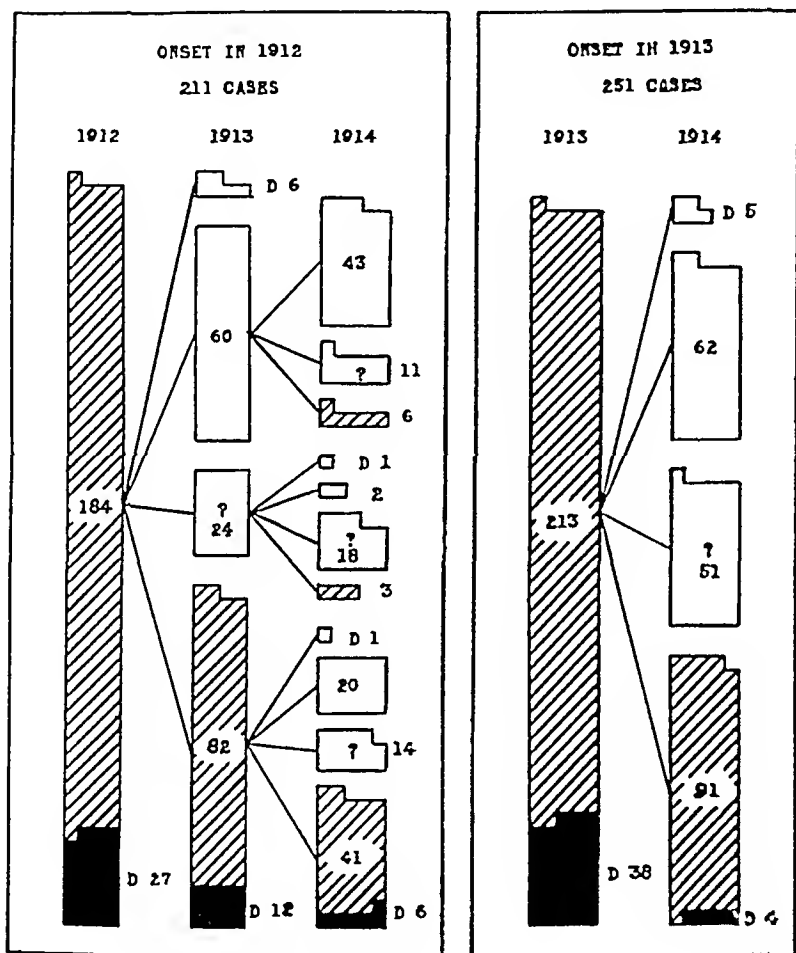


Fig. 9.—Behavior during subsequent years of pellagrins with onset in 1912 and 1913. The area of each polygon indicates the number of individuals in each respective group. The small squares represent individuals.

Those pellagrins who survived the second year of the disease without recurrent attack were further subdivided in Table 12, according to their behavior in the third year; fifteen of them had suffered recurrence in the third year. For nine of the fifteen there are records for a fourth year. The behavior of these nine pellagrins during the fourth year is summarized in Table 16. Of these nine patients, one, Pellagrin 9, a white woman, died April 2, 1913, at the age of 34, without recurrence of pellagra in that year. One, a colored woman, has an uncertain

record for the fourth year. Of the remaining seven patients, three, or 42.9 per cent., suffered recurrence in the fourth year and four, or 57.1 per cent., survived the year without recurrence. There were no deaths among the recurrent cases.

The subsequent behavior of this group may be disposed of here at once, because the number of individuals is too small to warrant further tabulation. Of the eight survivors, six had their initial attack in 1911 and records of their further behavior are not available for this study. Of the other two patients, one, Pellagrin 234, a colored woman, with uncertain record in the fourth year, has an uncertain record in the fifth year also and nothing further; the other patient, Pellagrin 80, a white woman, with onset in 1909 at age of 26, no recurrence in 1910, recurrence in 1911 and no recurrence in 1912, remained well and free from recurrence in the fifth and sixth years of her disease, namely, 1913 and 1914.

TABLE 17.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED THE SECOND AND THIRD YEARS WITHOUT ANY RECURRENCE

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	1	0	0	1	0	0
1908	2	1	0	1	0	0
1909	5	1	0	4	0	0
1910	14	2	0	12	0	0
1911	41	7	1	33	0	1
Totals	63	11	1	51	0	1

The 106 pellagrins who survived the third year without having any recurrence in either the second or the third year (Table 12) are of peculiar interest. Does an interval of two years without symptoms warrant the conclusion that the patient has recovered from pellagra? The subsequent behavior of this group has a bearing on this question. Of the 106 pellagrins, there were forty-three with initial attack in 1912, the record of whose behavior in the fourth year of pellagra is not available for this study. The behavior of the remaining sixty-three is summarized in Table 17. One of the patients had an indefinite record in the fourth year. Of the remaining 62, there were fifty-one, or 82.3 per cent., who survived the fourth year also without recurrence, and

eleven pellagrins, 17.7 per cent. of the sixty-two, who suffered recurrence in the fourth year after an interval of two years without definite symptoms of pellagra. It may be of interest to note here that all the eleven patients of this group who had recurrence of the disease in the fourth year were white women. There was one death among the eleven pellagrins with recurrence, 9.1 per cent.

TABLE 18.—COMPARATIVE BEHAVIOR DURING THE FOURTH YEAR OF THE FOUR GROUPS OF PELLAGRINS CONSIDERED IN TABLES 14, 15, 16 AND 17

Table Reference	Previous History of Patients	Behavior in the Fourth Year		
		Recurrences, per Cent.	Deaths in Recurrence, per Cent.	Survivors without Recurrence, per Cent.
14	Recurrences in both second and third years.....	78.6	13.2	21.4
15	Recurrence in second year; no recurrence in third.....	16.7	0.0	83.3
16	No recurrence in second year; recurrence in third.....	42.9	0.0	57.1
17	No recurrence in either second or third third year.....	17.7	9.1	82.3

The comparative behavior of the four groups of pellagrins considered in Tables 14, 15, 16 and 17 is summarized on the basis of percentage in Table 18. This table indicates very definitely that absence of a recurrence in any year is a sign of much better prognosis as far as life is concerned during subsequent years. It also indicates that an absence of recurrence in one year improves very much the prognosis in respect to freedom from the disease in the following year. In the groups shown in Tables 15 and 16 the patients with good health in the fourth year were 83.3 and 82.3 per cent., respectively, about the same proportion of escapes from recurrence as was shown during the third year by those who escaped recurrence in the second year (Table 12), for whom the analogous figure was 86.9 per cent.

In order to complete the consideration of all this series of pellagrins during the fourth year, there is presented in Table 19 a summary of the behavior of those patients for whom the record was indefinite in either the second or the third year or in both. This group includes the twenty-nine patients without definite record from Table 11, the analogous fifteen patients from Table 12 and all the sixty survivors from Table 13. The group is diminished by the loss of those with initial attack in 1912, because their history during the fourth year is not available, and as a result there remain only fifteen in the lot from Table 11, four from Table 12 and thirty-seven from Table 13, a total

of fifty-six cases. Of these fifty-six cases, there were thirty-nine with uncertain record in the fourth year, ten with recurrences and six survivors without recurrence in the fourth year; four died in recurrent attacks and one died without recurrence. The table shows how frequently a year with indefinite or uncertain record was followed by one in which there was a frank attack of pellagra or definite freedom from symptoms. Of course, most of the patients in this group gave very uncertain and indefinite histories for several years in succession.

The number of pellagrins remaining for consideration in the fifth year of the disease is rather small, and when grouped according to their behavior in preceding years, a considerable number of groups require consideration. The more important of these groups will be tabulated.

TABLE 19.—BEHAVIOR DURING THE FOURTH YEAR OF THE DISEASE OF THOSE SURVIVING PELLAGRINS WHOSE RECORD WAS INDEFINITE IN ANY PRECEDING YEAR

Year of Onset	Pellagrins in This Category	Behavior in the Fourth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	10	1	1	0	1	8
1908	2	1	0	0	0	1
1909	4	1	0	0	0	3
1910	8	3	1	0	0	5
1911	32*	4	2	6	0	22*
Totals	56*	10	4	6	1	39*

* Including one white child, sex unknown.

By referring to Table 14 it will be seen that 114 pellagrins had definite attacks of pellagra in four consecutive years. Of these, fifteen died in the fourth year. Of the remaining ninety-nine, there were thirty-one with onset in 1911, for whom data in regard to the fifth year are not available. There remain only sixty-eight of this group for consideration. Their behavior during the fifth year of the disease is summarized in Table 20. As is shown in the table, four of the sixty-eight were without definite record during the fifth year and one died without recurrence. Of the remaining sixty-three, there were forty-eight, or 76.2 per cent., who had recurrence in the fifth year and fifteen, or 23.8 per cent., survived without recurrence. Among the forty-eight with recurrent attack, there were four deaths, 8.3 per cent., which is the lowest mortality rate so far in this series of cases with annual recurrence of pellagra.

The patients who had recurrences in the second and third years, but survived the fourth year without recurrence, numbered thirty-one. Only fifteen of these can be considered in the fifth year because the other sixteen had their initial attacks in 1911. The behavior of these fifteen pellagrins during the fifth year is summarized in Table 21. Of the fifteen patients, three have an indefinite record for the fifth year, one had a recurrence and eleven survived without recurrence. There were two negro women in this group; one of them had a recurrence and the other an indefinite record for the fifth year. Of the nine white pellagrins, five female and four male, one woman had an indefinite record in the fifth year and the remaining eight survived without recurrence in that year. The figures are small, but they indicate a very good

TABLE 20.—BEHAVIOR DURING THE FIFTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED ANNUAL ATTACKS OF PELLAGRA FOR THE FIRST FOUR YEARS

Year of Onset	Pellagrins in This Category	Behavior During the Fifth Year				
		Recurrences	Deaths In Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	21	19	4	2	0	0
1908	7	7	0	0	0	0
1909	11	5	0	5	0	1
1910	29	17	0	8	1	3
Totals	68	48	4	15	1	4

prognosis for patients who experience a year without recurrence after having suffered three consecutive annual attacks of pellagra. Of the twelve patients with definite record, one, or 8.3 per cent., had recurrence and eleven, or 91.7 per cent., escaped recurrence. There were no deaths in this group in the fifth year.

The subsequent history of these patients to the end of 1914 will be considered here, inasmuch as they are so few. For the cases incident in 1910 the fifth year ends the history and there are only four others. One of these, Pellagrin 124, a white woman, with onset in 1909, recurrence in 1910 and 1911, no recurrence in 1912 and indefinite record in 1913 (the fifth year), survived the sixth year, 1914, without recurrence. Another, Pellagrin 781, a white man, with onset in 1906, recurrence in 1907 and 1908 and no recurrence in 1909 and 1910 (the fifth year), survived without any further recurrence of the disease to the end of 1914, the ninth year of his disease. A third case, Pellagrin 633, a white man, with onset in 1900, recurrences in 1901 and 1902, no recurrence in 1903 and 1904 (the fifth year), remained free from recurrence also

in 1905, 1906, 1907, 1908 and 1909, had recurrences in 1910 (the eleventh year of the disease), 1911 and 1912, and survived without recurrence in 1913 and 1914 (the fifteenth year of his disease). This patient was an inmate of a hospital for the insane in 1912 and part of 1913. The fourth patient in this residual group, Pellagrin 533, a white woman, with onset in 1893, recurrence in 1894 and 1895, no recurrence in 1896 and 1897 (the fifth year), remained free from recurrence until 1913 (the twenty-first anniversary of her initial attack), the interval of good health being eighteen years. In 1913 she had a recurrence and she survived without recurrence in 1914. This patient was seen in August, 1915, at which time she was still in good health and had experienced no further return of the disease. The significance of these observations will be considered in a subsequent part of this paper.

TABLE 21.—BEHAVIOR DURING THE FIFTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO HAD RECURRENT ATTACKS IN THE SECOND AND THIRD YEARS AND SURVIVED WITHOUT RECURRENCE IN THE FOURTH YEAR

Year of Onset	Pellagrins in This Category	Behavior During the Fifth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	3	0	0	3	0	0
1908	0	0	0	0	0	0
1909	1	0	0	0	0	1
1910	11	1	0	8	0	2
Totals	15	1	0	11	0	3

Reference to Table 15 will show that seven pellagrins survived a recurrence in the fourth year, after having a recurrence in the second year and no recurrence in the third. Only three of these seven patients had their initial attacks before 1911 and these three had their onset in 1910. One of them, Pellagrin 201, a white woman, has an indefinite record in 1914, the fifth year of her disease. Another, Pellagrin 112, a white woman, remained free from recurrence in 1914. The third, Pellagrin 282, a white woman, had a recurrence in 1914.

Table 15 also shows thirty-five pellagrins surviving the fourth year without recurrence, after recurrence in the second year and no recurrence in the third. Only eleven of these patients had their initial attacks before 1911 and eight of these arose in 1910. One of the eight, Pellagrin 131, a white man, is without definite record in 1914, the fifth

year. The other seven were white women; three of them had recurrences in the fifth year (1914) and four survived without recurrence. Of the three cases with onset previous to 1910, one, Pellagrin 643, a white woman, with onset in 1909, survived without recurrence in 1913 and 1914, the fifth and sixth years of her disease. The two others, Pellagrins 200 and 432, both white women, had their initial attacks in 1908. The former survived without recurrence in 1912 and 1913 and her record for 1914 (the seventh year of her disease) is uncertain. The latter, Pellagrin 432, had no recurrence in 1912 (the fifth year), but suffered a recurrence in May, 1913, within a few days after childbirth, and also had a recurrence in 1914. Of the ten cases with definite record in the fifth year, three, or 30 per cent., had recurrence and seven, or 70 per cent., survived without recurrence. There were no deaths recorded in this group.

TABLE 22.—BEHAVIOR DURING THE FIFTH YEAR OF THOSE SURVIVING PELLAGRINS WHOSE RECORD WAS INDEFINITE IN ANY PRECEDING YEAR

Year of Onset	Pellagrins in This Category	Behavior During the Fifth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	9	2	1	0	0	7
1908	2	1	0	0	0	1
1909	5	1	0	1	0	3
1910	12	2	0	2	0	8
Totals	28	6	1	3	0	19

The survivors after the fourth year of the group of pellagrins with no recurrence in the second year, but with recurrence in the third year, have been discussed in detail in the text in connection with Table 16 (see page 360).

Reference to Table 17 shows eleven pellagrins who survived a recurrent attack in the fourth year, after freedom from symptoms during the second and third years. All were white women. Only four of them had the initial attack previous to 1911. One of these, Pellagrin 654, with onset in 1910, was free from recurrence in the fifth year of the disease, 1914. Another, Pellagrin 544, with onset in 1910, was without definite record in 1914. A third, Pellagrin 178, with onset in 1909, suffered a recurrence in 1913 (the fifth year), but escaped recurrence in 1914, being pregnant during the spring and summer. The fourth patient, Pellagrin 166, with onset in 1908, suffered a recurrent

attack in the fifth year, 1912, but survived without recurrence in 1913 and 1914, the sixth and seventh years of the disease.

In Table 17 there were fifty-one survivors of the fourth year without any recurrence after the year of onset. Of these, eighteen had the initial attack previous to 1911, so that further history is available. Nine of them were white women with onset in 1910; of these, seven were without recurrence in the fifth year (1914) and one, Pellagrin 860, suffered a recurrence early in 1914 (the fifth year), about five weeks

TABLE 23.—COMPARATIVE BEHAVIOR DURING THE FIFTH YEAR OF THE 115 PELLAGRINS WITH DEFINITE RECORD IN THE FIFTH YEAR, GROUPED ACCORDING TO THEIR RECORD IN PRECEDING YEARS

Table Reference	Recurrences in Previous Years			Number of Cases	Recurrences		Deaths		Living without Recurrence	
	2d	3d	4th		Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
20	+	+	+	63	48	76.2	4	8.3	15	23.8
21	+	+	0	12	1	8.3	0	0.0	11	91.7
	+	0	+	2	1	50.0	0	0.0	1	50.0
	+	0	0	10	3	30.0	0	0.0	7	70.0
	0	+	+	0	0	0	0
	0	+	0	1	0	0.0	0	0.0	1	100.0
	0	0	+	3	2	66.7	0	0.0	1	33.3
	0	0	0	15	2	13.3	1	50.0	13	86.7
Total, history definite.....	106	57	53.8	5	8.8	49	46.2
Indefinite in any year (22)	9	6	66.7	1	16.7	3	33.3
Totals.....	115	63	54.8	6	9.5	52	45.2

before giving birth to a child, and she died of pellagra June 21, 1914. The other patient, Pellagrin 437, was without definite record in 1914. Three of the group of eighteen were white men with onset in 1910, of whom two remained free from recurrence in the fifth year, 1914, and one, Pellagrin 104, was without definite record in that year. Four of the eighteen were white women with onset in 1909, Pellagrins 119, 422, 644 and 817. Pellagrin 119 was without definite record in 1913 and 1914, having moved away. Pellagrins 422 and 817 survived without recurrence in 1913 and 1914, the fifth and sixth years of the disease. Pellagrin 644 suffered a recurrence in the fifth year (1913), but remained free from recurrence in 1914. This last case is an example

of recurrence (or of a second onset?) after three years without symptoms. One of the group of eighteen, Pellagrin 1124, a white woman, had her initial attack in 1908. She escaped recurrence in the fifth, sixth and seventh years of the disease (1912, 1913 and 1914) as well as in the earlier years. This case is possibly a valid example of complete recovery after a single attack of pellagra. The last remaining case in the group, Pellagrin 689, a white woman, had her initial attack in 1905 and remained without recurrence up to and including 1914, the tenth year. This case is another possible example of recovery after one attack. Her history is vouched for by a very reliable physician who has had a large experience with pellagra in Spartanburg County and has had this patient continuously under observation. Of the whole eighteen pellagrins without recurrence to the end of the fourth year, there were three without definite record in the fifth year, two with recurrence, one of which resulted in death, and thirteen without recurrences in the fifth year. Of the fifteen with definite record, thirteen, or 86.7 per cent., continued free from symptoms in the fifth year.

TABLE 24.—BEHAVIOR DURING THE SIXTH YEAR OF THOSE PELLAGRINS WHO SURVIVED ANNUAL ATTACKS OF PELLAGRA FOR THE FIRST FIVE YEARS

Year of Onset	Pellagrins in This Category	Behavior During the Sixth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	15	15	0	0	0	0
1908	7	6	0	1	0	0
1909	5	5	0	0	0	0
Totals	27	26	0	1	0	0

By reference to Table 19 it will be seen that fifty-three Pellagrins who had indefinite record for either the second or the third year or both survived the fourth year. Of these, twenty-one had their initial attacks before 1911 and are, therefore, available for consideration in the fifth year of the disease. To these twenty-one may be added six with indefinite record in the fourth year, from Table 14, one from Table 15, one from Table 16 and none from Table 17, making a total of 29 patients with uncertain record in one or more previous years, to be considered in the fifth year of the disease. The behavior of these cases during the fifth year is summarized in Table 22. Twenty of the twenty-nine had indefinite record in the fifth year, six had recurrent attacks, with one death, and three survived the fifth year without recurrence. There were only nine pellagrins of this group with definite

record in the fifth year, 66.7 per cent. of them having recurrence and 33.3 per cent. surviving without recurrence. There was one death among the six with recurrent attacks, 16.7 per cent.

Table 23 shows in summary a comparison of the behavior during the fifth year of the different groups determined by behavior in previous years. Many of the groups are too small for the percentage figures to be significant. The group with annual recurrence in consecutive years includes sixty-three pellagrins and shows a recurrence rate of 76.2 per cent., which is higher than for any other group. The death rate in recurrence in this group was 8.3 per cent., four deaths in forty-eight recurrences, a mortality rate considerably lower than that for the initial attack or for earlier recurrences. Among the forty-three pellagrins who escaped recurrence in one or more of the first four years of the disease (all the remaining groups with definite history) there were only nine recurrent attacks in the fifth year, 20.9 per cent., and only one death, 11.1 per cent. of those with recurrence. For the thirty-eight who escaped recurrence in the fourth year, the prognosis for the fifth year appeared to be particularly good, as only six of them, 15.8 per cent., suffered recurrence in the fifth year.

TABLE 25.—BEHAVIOR DURING THE SIXTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHOSE RECORD WAS INDEFINITE IN ANY PRECEDING YEAR .

Year of Onset	Pellagrins in This Category	Behavior During the Sixth Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	8	3	0	0	1	4
1908	2	1	0	0	0	1
1909	8	0	0	4	0	4
Totals	18	4	0	4	1	9

The only pellagrins in this series whose histories have not already been traced to the end of the record are those included in Tables 20 and 22. In Table 20 there were shown forty-eight pellagrins with recurrent attacks every year up to and including the fifth year of the disease. Of these, forty-four survived the fifth year and for twenty-seven of them the record extends to the sixth year. The behavior of these twenty-seven survivors is summarized in Table 24. In twenty-six of the twenty-seven cases, or 96.3 per cent., the disease recurred in the sixth year, with no deaths, and in one, or 3.7 per cent., there was freedom from recurrence in the sixth year. This one patient, Pellagrin 277, a white woman, also remained free from recurrence in 1914, the

seventh year of her disease. Of the fifteen pellagrins of Table 20, who survived the fifth year without recurrence, seven have further records. Pellagrin 444, a white woman, with onset in 1907, recurrences in 1908, 1909 and 1910 and freedom from recurrence in 1911 (the fifth year), survived without recurrence in 1912 and 1913, the sixth and seventh years, but suffered recurrence in 1914, the eighth year of her disease. Pellagrin 642, a white woman, with onset in 1904, recurrences in 1905, 1906 and 1907 and freedom from recurrence in 1908 (the fifth year), remained free from recurrence through 1913 (the tenth year), but suffered recurrence (or a new onset?) in 1914, the eleventh year of her disease, and died of pellagra in September, 1914. The remaining five of this group were also all white women and their initial attacks occurred in 1909. Pellagrins 94 and 163 suffered recurrence in the

TABLE 26.—SUBSEQUENT BEHAVIOR OF EIGHT PELLAGRINS WHO SURVIVED THE SIXTH YEAR AFTER HAVING AN INDEFINITE RECORD IN ANY PRECEDING YEAR

Pellagrin	Onset	Recurrence in Subsequent Years					
		7th	8th	9th	10th	11th	12th
1187	1900	+	?	?	+	+	+ D
296	1903	+	+ D				
285	1903	?	+ D				
774	1904	?	+ D				
1024	1905	+	+	+	+		
70	1905	?	+	+ D			
543	1906	?	?	0			
207	1907	+	?				

sixth year (1914) and Pellagrins 151, 128 and 59 survived the sixth year (1914) without recurrence. In the sixth year, therefore, five, or 71.4 per cent. of the seven, remained free from recurrence and two, or 28.6 per cent., suffered recurrence, with no deaths in the sixth year.

The one surviving pellagrin with indefinite record for the fifth year in Table 20, for whom further record is available, and the fifteen surviving pellagrins of Table 22, with onset before 1910, constitute a group of pellagrins with uncertain record in some one of the first five years, whose subsequent behavior is still to be discussed. To these fifteen cases may be added also Pellagrin 124, with indefinite record in the fifth year (Table 21 and accompanying text), and Pellagrin 119 (discussed on page 366), making eighteen patients in all, with indefinite record in one or more years previous to the sixth. Their behavior in

the sixth year is summarized in Table 25. Of the eighteen pellagrins, nine had an indefinite record in the sixth year and one died without recurrence; eight had definite records, four having recurrences and four surviving without recurrence in the sixth year. There were no deaths in recurrent attacks. The two patients with onset in 1908 in Table 25 were Pellagrin 22, a white man, and Pellagrin 1,229, a white woman. The former had a recurrence again in 1914, the seventh year of his disease, and the latter was again without definite record in the seventh year. The eight surviving patients in this table with onset in years previous to 1908 had their initial attacks in various years. Their behavior after the sixth year to the end of the record is shown in Table 26. In the seventh year three had recurrences and five had indefinite records. In the eighth year five had recurrences, three of them dying, and three had indefinite records. In the ninth year two had recurrences, one dying; one escaped recurrence and one had indefinite record. In the tenth year one had recurrence and the other an indefinite record. This last-mentioned case, Pellagrin 1,187, had recurrences in the eleventh and twelfth years, dying in the latter year. Three of these eight patients remained alive at the end of 1914.

TABLE 27.—BEHAVIOR DURING THE SEVENTH YEAR OF THE DISEASE OF THOSE PELLAGRINS WHO SURVIVED ANNUAL ATTACKS OF PELLAGRA DURING SIX CONSECUTIVE YEARS

Year of Onset	Pellagrins in This Category	Behavior in the Seventh Year				
		Recurrences	Deaths in Recurrence	Living without Recurrence	Dying without Recurrence	Without Definite Record
Before 1908	15	14	1	1	0	0
1908	6	5	0	1	0	0
Totals	21	19	1	2	0	0

In Table 24 there were shown twenty-one pellagrins with onset before 1909 who survived annual attacks of pellagra during six consecutive years. The behavior of these patients during the seventh year of the disease is summarized in Table 27. Of the twenty-one pellagrins, nineteen, or 90.5 per cent., had recurrences in the seventh year and two, or 9.5 per cent., survived without recurrence in this year. There was one death in recurrent attack, indicating a mortality rate of 5.3 per cent. One of those who escaped recurrence, Pellagrin 51, a white woman, had her first attack in 1907. She also escaped recurrence in 1914, the eighth year of her disease. The other twelve sur-

vivors with onset before 1908 had their initial attacks in various years. Their behavior in the later years of the disease up to the end of the record in 1914 is shown in Table 28. Of the twelve patients, nine had recurrences in the eighth year and three had indefinite record. In the ninth year, nine patients remained to be considered. Eight of them had recurrences, one dying, and one had an indefinite record. Of the seven patients remaining for consideration in the tenth year, one died without recurrence, one survived without recurrence and five suffered recurrence. In the eleventh year all of the four patients with available records had recurrence and one of them committed suicide by drowning. Beyond the eleventh year only one pellagrin remained for consideration. He suffered recurrence every year to and including 1912, the twenty-first year of his disease, and died early in 1913 without recurrence in the latter year.

TABLE 28.—SUBSEQUENT BEHAVIOR OF TWELVE PELLAGRINS WHO SURVIVED ANNUAL ATTACKS OF PELLAGRA DURING SEVEN CONSECUTIVE YEARS

Pellagrin	Onset	Recurrence in Subsequent Years							
		8th	9th	10th	11th	12th	13th	14th	15th
20	1892	+	+	+	+	+	+	+	+
286	1898	+	+	+	+				
354	1901	+	+	‡					
145	1904	+	+	+	+				
996	1904	+	+	+	+				
168	1905	+	+	+					
563	1905	+	+	0					
582	1905	+	+ D						
205	1906	?	?						
445	1907	+							
659	1907	?							
421	1907	?							

* Pellagrin 20 suffered recurrence every year to and including 1912, the twenty-first year of the disease. He died Feb. 27, 1913, without recurrence in 1913.

† Died, suicide.

‡ Died without recurrence.

Inasmuch as the group of pellagrins with onset before 1908 has been discussed in various places in the preceding pages, the data in regard to the behavior of this group according to the year of the disease are summarized in Table 29 to the end of the fifteenth year. The records of only two cases extend beyond that year. Pellagrin 20, a white man, with onset in 1892, continued to suffer recurrences every year from the sixteenth to the twenty-first year, inclusive, and he died early

in the twenty-second year of the disease, without a recurrence in that year. Pellagrin 533, a white woman, with onset in 1893, continued to be free from recurrence from the sixteenth to the twentieth year, inclusive; she suffered a recurrence in the twenty-first year of her disease (1913) and survived without recurrence the twenty-second year.

TABLE 29.—BEHAVIOR OF PELLAGRINS WITH ONSET BEFORE 1908 IN THE YEARS SUBSEQUENT TO THE INITIAL ATTACK

	Year													
	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Recurrences.....	32	28	24	21	18	17	15	10	7	7	3	2	1	1
Deaths in recurrence..	4	1	3	5	0	1	3	2	0	2	1	0	0	0
Living without recurrence.....	1	1	4	6	6	7	6	6	5	1	1	1	2	2
Dying without recurrence.....	1	0	1	0	1	0	0	0	1	0	0	0	0	0
Indefinite record.....	10	10	9	7	4	4	6	2	0	0	0	0	0	0

COMMENT

From the records of these cases in the successive years of their disease it is possible to draw certain deductions of general application to the prognosis of pellagra. Considering only those with definite records and with a history of attack in each year after onset, we obtain the figures shown in Table 30. One striking feature of these data is the evident increased tendency for recurrence to appear with greater certainty after the habit has become established. The lowest recurrence rate, 70.8 per cent., occurred in the year following the initial attack. From the third to the fifth year the recurrence rate was between 75 and 80 per cent., and after the fifth year it was constantly above 90 per cent. Another important feature is the death rate in recurrence, which is consistently lower than the death rate in initial attack, which was 15.8 per cent. for the entire series of cases. From the second to the fourth year, inclusive, the death rate in recurrence was between 12.5 and 13.5 per cent. After the fourth year it remained consistently below 10 per cent., except where the number of individuals became so small that a single death gave a higher percentage. For all recurrences after the fourth year added together (129) there were only seven deaths, indicating a death rate of 5.4 per cent. for these years. This fact is in direct conflict with the statement commonly made in textbooks that the prognosis in an attack of pellagra is less favorable in the later years of the disease. As far as life is concerned and as far as recovery from that one attack is concerned, the prognosis would appear from

our data to be distinctly better in the later years. On the other hand, the prognosis in respect to freedom from recurrence in subsequent years would appear to be less favorable in the later years for those with consecutive annual recurrences. The improved prognosis in respect to life cannot be ascribed to the increasing age of the patients, because, as we have already shown in a study² of a part of these patients, the death rate is higher in older pellagrins in both initial and recurrent attacks.

TABLE 30.—TENDENCY TO RECURRENCE AND DEATH RATE IN RECURRENCE IN SUCCESSIVE YEARS FOR PELLAGRINS WITH CONSECUTIVE ANNUAL ATTACKS

	Year											
	2	3	4	5	6	7	8	9	10	11	12	13-21
Pellagrins considered...	681	292	144	63	27	21	9	8	5	4	1	9*
Recurrences.....	482	228	113	48	26	19	9	8	5	4	1	9*
Recurrences, per Cent...	70.6	78.1	78.5	76.2	96.3	90.5	100	100	100	100	100	100
Deaths in recurrence...	63	29	15	4	0	1	0	1	0	1	0	0
Death rate, per Cent....	13.1	12.7	13.3	8.3	0.0	5.3	0.0	12.5	0.0	25.0	0.0	0.0

* Pellagrin 20 continued to have recurrences each year to the twenty-first year. He died in the twenty-second year without recurrence.

Those pellagrins who escaped recurrence every year after the year of onset up to the year of a definite observation serve as a criterion of recovery after a single attack. The rate of recurrence and the death rate among those who had recurrence for the patients in this category are indicated in Table 31. The number of individuals in this category is small, especially after the fifth year of the disease. Up to the fifth year, however, the figures are significant and they indicate very clearly that a person who has had an initial attack of pellagra and then escaped recurrence altogether for one, two or three years has about fifteen chances in a hundred of suffering a recurrence in the next following year. Furthermore it would seem to make very little difference whether the interval without symptoms had been one, two or three years, as the recurrence rate was between 13 and 18 per cent. in all three of these groups.

Those patients who escaped recurrence in a single year after an unbroken series of annual attacks of pellagra may be worthy of special attention also. Thus in the third year there are definite records for 122 pellagrins who had escaped recurrence in the second year. In the fourth year there are definite records for forty-two individuals who suffered an attack in the first year and again in the second, but escaped

2. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Prognosis in Pellagra, Proc. New York Path. Soc., 1915, xv, 30.

recurrence in the third year. What is the effect of this one year's freedom from recurrence on the prognosis for the following year? The data on this question are summarized in Table 32. The number of cases in this category is also quite limited, but for three years there are enough cases to be somewhat significant. Of the 122 patients who escaped recurrence in the second year, sixteen, or 13.1 per cent., had recurrence in the third year. Of the forty-two who had recurrence in the second year and escaped recurrence in the third year, 16.7 per cent. suffered recurrence in the fourth year. Of the twelve patients with

TABLE 31.—TENDENCY TO RECURRENCE AND DEATH RATE IN RECURRENCE IN SUCCESSIVE YEARS FOR PELLAGRINS WITHOUT RECURRENCE FROM YEAR OF ONSET TO YEAR OF OBSERVATION WITH DEFINITE RECORD

	Year of the Disease							
	3	4	5	6	7	8	9	10
Pellagrins considered.....	122	62	15	4	2	1	1	1
Recurrences.....	16	11	2	0	0	0	0	0
Recurrences, per cent.	13.1	17.7	13.3	0.0	0.0	0.0	0.0	0.0
Deaths in recurrence.....	1	1	1	0	0	0	0	0
Death rate, per cent.	6.3	9.1	50.0

TABLE 32.—TENDENCY TO RECURRENCE AND DEATH RATE IN RECURRENCE IN SUCCESSIVE YEARS OF THE DISEASE FOR PELLAGRINS WHO HAVE HAD ONLY A SINGLE YEAR WITHOUT RECURRENCE IMMEDIATELY PRECEDING THE RESPECTIVE YEAR

	Year of the Disease					
	3	4	5	6	7	8
Pellagrins considered.....	122	42	12	7	1	1
Recurrences.....	16	7	1	2	0	0
Recurrences, per cent.	13.1	16.7	8.3	28.6	0	0
Death in recurrence.....	1	0	0	0	0	0
Death rate, per cent.	6.3	0.0	0.0	0.0

recurrence in the second and third years, but without recurrence in the fourth year, only one, or 8.3 per cent., suffered recurrence in the fifth year. The prognosis in respect to recurrence has been as good for these patients as for those who had no recurrence at all after the year of onset, shown in Table 31. From both these tables it is evident that freedom from recurrence in a single year renders the prognosis for the next year very good, as more than 80 per cent. of such patients escaped for the next year also. These data do not indicate any better prog-

nosis for those who have escaped recurrence for two or more consecutive years than for those who have escaped for a single year.

In the entire series of cases there were twenty-three patients who suffered recurrence after two or more consecutive years of freedom from recurrence. Four of these had their initial attacks previous to 1908. The other nineteen can be located on the charts. Fourteen of these were instances of recurrence after two years of freedom from attack, five after three years of freedom from attack, two after six years, one after seven years and one after seventeen years without recurrence. Among these twenty-three patients there were four who died in that new recurrent attack, one after two years without recurrence, one after three years without recurrence and two after six years without recurrence. The death rate of 17.8 per cent. (four out of twenty-three) for the group is rather high, indicating a poor prognosis for those pellagrins who suffer recurrence after an interval of several years without erythema.

SUMMARY

1. The total number of recorded recurrent attacks of pellagra in this series of patients was 1,053, with 130 deaths in the year of recurrence. The death rate in recurrence was therefore 12.3 per cent.

2. The total number of instances of freedom from recurrent attack of pellagra during a year numbered 617. The ratio of nonrecurrence to recurrence was therefore 617 to 1,053, or approximately 4 to 7.

3. For pellagrins in the later years of the disease the prognosis is more favorable for recovery from the present attack but apparently less favorable in respect to escape from recurrence in the next subsequent year. In other words, after successive annual attacks the disease seems to become more firmly established as a chronic disease with annual manifestations, but also becomes less acutely malignant.

4. A year without recurrence is a very favorable omen. Subsequent recurrence is less likely to appear and if it does appear it is less likely to end in death.

5. Recurrence after several years of freedom from the disease is not uncommon and a considerable proportion of these recurrences end fatally.

6. It is impossible to say when a patient has definitely recovered from the disease pellagra. It seems to us very much more advisable to speak of recovery from the particular attack of the disease in a given year. In those patients who escape recurrence for one or more years it is best to consider the disease as arrested or as inactive, much as we do in tuberculosis or in syphilis.

THE TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

WITH INTRAVENOUS SALVARSAN ALONE, WITH INTRAVENOUS SALVARSAN AND INTRASPINAL SALVARSANIZED SERUM TOGETHER AND WITH INTRASPINAL SALVARSANIZED SERUM ALONE *

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BOSTON

Since Swift and Ellis first published their method of intraspinal treatment with salvarsanized serum for patients with syphilis of the central nervous system, much has been written by many observers both in favor of and against the method of Swift and Ellis. These opposite opinions probably to a certain extent have resulted from the limited amount of experience each observer has had with this treatment, as the majority of reports have been based on a few cases, without using other methods for control. It is obvious that in treating a few cases by the same method one observer might meet only favorable cases, while another observer might meet unfavorable ones. A fairer estimate of the value of the method would seem to be obtained from a large series of variously treated cases which have been carefully followed during treatment and which have been under observation for some time since the treatment was stopped. It is with this in mind that we report in detail on all the cases treated by the three methods, intravenous salvarsan alone, intraspinal salvarsanized serum alone, and both intravenous salvarsan and intraspinal salvarsanized serum, at the Peter Bent Brigham Hospital since its opening three years ago, in order to compare the results following each method.

Seventy-five patients with the following diagnoses have been treated: forty-eight cases of tabes dorsalis, six of general paresis of the insane, sixteen cases of cerebrospinal syphilis, and five of syphilitic meningitis. To these patients 450 intraspinal injections of salvarsanized serum and 350 doses of salvarsan were given. In this paper for means of comparison the cases are grouped according to the way the patients were treated, so that all cases naturally fall into one of the three following groups: in group 1 are those cases in which the patients were treated with intravenous salvarsan alone; in group 2 are those in which the patients were treated with both intravenous salvarsan and

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* From the Medical Clinic of the Peter Bent Brigham Hospital.

intraspinal salvarsanized serum; and in group 3 are those cases in which the patients were treated with intraspinal salvarsanized serum only, no other medication being used.

At first all patients with central nervous system syphilis were treated with salvarsan alone; but if, as happened in many cases, four or six injections of salvarsan were not followed by much improvement in the symptoms or by a change in the Wassermann reaction and in the cell count in the spinal fluid, these patients were then given salvarsanized serum intraspinally in conjunction with the intravenous salvarsan. This double method of treatment was followed usually by improvement in both the clinical symptoms and the laboratory findings. Since the intraspinal salvarsanized serum seemed to reinforce salvarsan alone, we desired to determine if there was actually any value in the intraspinal salvarsanized serum itself. We therefore selected patients with negative Wassermann reactions in the blood serum, but with positive findings in the spinal fluid, for intraspinal treatment with salvarsanized serum alone. We felt justified in this procedure, since many patients had not improved under salvarsan alone, and, furthermore, if such treatment should prove to be beneficial, three patients could be treated with one dose of salvarsan, that is, one with salvarsan and two with that patient's serum. Our hopes were realized, for we found that these selected patients improved from every viewpoint following the intraspinal treatment with salvarsanized serum alone. Therefore we have adhered to the following schedule: to patients with a positive reaction in both blood and spinal fluid, first, salvarsan alone is given; if satisfactory improvement does not follow, then salvarsanized serum is given intraspinally in conjunction with salvarsan; to those with a negative Wassermann reaction in the blood serum, but with positive findings in the spinal fluid, is given only intraspinal salvarsanized serum.

Drugs other than salvarsan¹ have been used very sparingly in these cases. Neosalvarsan was discontinued in the treatment of all cases of syphilis after a short trial, since the early stages of the disease did not yield to it as readily as to the original salvarsan and what improvement did follow its use was temporary. Mercury in the form of inunctions and intramuscular injections was employed very little because of the frequency of a falsely negative Wassermann reaction following its use. Morphine and aspirin were required in an occasional case to control the temporary reaction pains following intraspinal treatment. Other than the foregoing treatment no therapy was used.

All patients receiving intravenous salvarsan alone and all of those receiving intraspinal salvarsanized serum alone were required to remain

1. Recently diarsenol has been substituted for salvarsan.

in the hospital the night immediately following the treatment, but they were discharged the next morning. Those patients treated with both intravenous salvarsan and intraspinal salvarsanized serum were frequently given both treatments in the same afternoon, so that only one night was spent in the hospital; usually, however, these patients were given salvarsan on one afternoon and intraspinal salvarsanized serum on the next afternoon, in which case these patients remained in the hospital two nights.

During the first year and a half all patients, with some exceptions which will be mentioned, were treated at weekly intervals; but as this seemed to be too frequent in some cases, the interval between treatments was lengthened to three weeks in some patients and to irregular intervals in others. These longer intermissions between treatments were not followed by as rapid improvement as were the weekly periods, so that no definite rule has since been followed. Each case is a rule unto itself, but the best results seemed to follow frequent treatments.

Occasionally a patient experienced a marked reaction for eighteen or twenty hours following the intraspinal treatment, this reaction consisting of a severe aggravation of the pains experienced previous to treatment or a renewal of the pains complained of years previously. Such reactions could be avoided often by increasing the interval between treatments in that particular case. A moderate reaction, consisting of an aggravation of symptoms lasting for a few hours, is to be desired, as more improvement in every way followed than resulted when there was but a slight reaction or none at all. Frequently it is difficult to differentiate the different types of central nervous system syphilis on account of the vague symptoms and the absence of distinctive signs. However, in such cases the reaction following intraspinal treatment will cause an accentuation of indefinite symptoms and will revive forgotten symptoms, which will aid in making a diagnosis. Occasionally, after a severe reaction, the spinal fluid cell count was increased and many red blood cells were present, but if treatment was omitted for two weeks the cell count fell to its previous level, and the red blood cells disappeared.

The technic employed in the preparation of the salvarsanized serum was that described by Swift and Ellis, except that larger doses of intravenous salvarsan were given, these usually being 0.5 gm. and 0.6 gm., and the blood was withdrawn one half hour instead of one hour later; and for the intraspinal injection from 20 c.c. to 25 c.c. of whole serum instead of a 40 or 50 per cent. dilution of the serum with saline was used. These modifications should increase several times the amount of available salvarsan, or whatever it is present in the serum, over that obtained by the original method of Swift and Ellis. These

large amounts of serum withdrawn such a short time after the injection of salvarsan probably contain as much arsenic or salvarsan as has been found safe to inject by itself directly into the meninges.

The benefit from treatment and the indication for the best method of treatment to follow in each case were based on the resultant changes in the patients' symptoms and in the cell count and the Wassermann reaction of the spinal fluid. All observers agree that the Wassermann reaction in the spinal fluid is a dependable test and very resistant to changes by treatment. We have titrated all spinal fluids, using amounts of spinal fluid varying from 2 c.c. to 0.05 c.c. in each tube against a 0.4 per cent. cholesterin reinforced human heart antigen, and we have found that in untreated cases the spinal fluid gave fixation with the same amounts on successive tests and that cases with little treatment showed little or no effect on the intensity of fixation. Other observers agree that patients with central nervous system syphilis are prone to have periods of spontaneous improvement which may or may not be followed by remissions. Consequently, one must be very cautious in interpreting improvement as due to treatment. We have followed our patients with great care, always having in mind spontaneous improvement, and, furthermore, since our patients are under our observation indefinitely after treatment has stopped, we are able to verify or discredit our previous conclusions, so that we feel justified when we state that the patient showed improvement.

Just as there is universal agreement in the reliability and the constancy of a positive Wassermann reaction in the spinal fluid and universal agreement in the unreliability to a certain extent in symptomatic improvement due to treatment, so is there disagreement as to the value, constancy and interpretation of an increased cell count in the spinal fluid. In our cases of syphilitic meningitis the cell count varied from 500 to 9,800, and in one case, which was probably one of meningitis, the cell count was only 150; in these cases the predominating cell was of the small lymphoid variety, with a high percentage of the endothelial type of cell and a small percentage of the polymorphonuclear type. Under treatment the lymphoid type of cell relatively increased and the other types of cell absolutely decreased, thus leaving only the lymphoid cell, which slowly decreased to normal. In our cases of cerebrospinal syphilis, general paresis of the insane and tabes dorsalis the cell counts varied from 10 to 200. In the first two diseases the prevailing type of cell was the large endothelial variety, with a few of the small endothelial and small lymphoid types; under treatment the large endothelial cell rapidly decreased and the small types of cell slowly decreased. In the cases of tabes the small lymphoid cell was usually the only one present; occasionally a few small endothelial cells were noted. However, the number and type of cell were really of

TABLE 1.—COMPARISON BETWEEN THE EFFECT OF TREATMENT WITH SEVERAL DOSES OF INTRAVENOUS SALVARSAN AND WITH ONE INTRASPINAL INJECTION OF SALVARSANIZED SERUM

Cause Number*	Salvarsan in Grams at Weekly Intervals	Change in Cell Count	Change in Wassermann Reaction	Clinical Improvement	Intraspinal Serum, C.c.	Change in Cell Count
T. D. 1	0.1, 0.6, 0.6, 0.6, 0.6, 0.6	44 to 35	None	None	14	35 to 7
22	0.4, 0.6, 0.6, 0.6, 0.0, 0.6	7 to 7	None	Slight	20	7 to 6
3	0.3, 0.4, 0.5, 0.0, 0.6, 0.6	2 to 2	None	Slight		
2	0.3, 0.4, 0.6, 0.6, 0.6, 0.6	6 to 5	None	None		
G. S. 71	0.1, 0.0, 0.6, 0.6, 0.6, 0.6	51 to 7	0.8 c.c. + to 1.5 c.c. ±			
52	0.4, 0.6, 0.6, 0.6, 0.0, 0.6	98 to 29	0.3 c.c. + to 1 c.c. +	Headache relieved		
63	0.3, 0.4, 0.4, 0.4, 0.4	12 to 4	None			
T. D. 6	0.1, 0.4, 0.4, 0.4, 0.4	10 to 7	0.3 c.c. + to 0.1 c.c. +	None		
C. S. 7	0.3, 0.4, 0.6, 0.6, 0.6	6 to 6	None	Headache relieved		
T. D. 67	0.4, 0.4, 0.0, 0.0, 0.6	15 to 7	None	Slight		
C. S. 72	0.3, 0.0, 0.6, 0.6, 0.0	30 to 27	None	None	16	30 to 10
T. D. 30	0.4, 0.5, 0.6, 0.6	32 to 32	None	None		
M. 37	0.3, 0.5, 0.6, 0.6	940 to 33	0.5 c.c. + to 1 c.c. +	Stiff neck, positive Kernig's relieved		
23	0.3, 0.4, 0.0	550 to 553	None	Headache relieved	20	533 to 272
T. D. 20	0.3, 0.5, 0.5	16 to 15	None	None	16	15 to 57
C. S. 18	0.3, 0.4, 0.5	80 to 81	None	None	16	81 to 40
10	0.3, 0.4, 0.6	39 to 47	None	None	18	47 to 55
45	0.3, 0.5, 0.6	15 to 14	None	None	18	14 to 5
T. D. 28	0.4, 0.5, 0.0	100 to 80	None	None	18	80 to 37
47	0.3, 0.4, 0.4	80 to 21	None	None	20	21 to 7
49	0.3, 0.6, 0.6	37 to 01	None	Diplopia relieved	23	61 to 30
O. S. 52	0.4, 0.6, 0.6	98 to 60	0.3 c.c. + to 1 c.c. +	Much improvement		

T. D.	0.3, 0.4, 0.4	0.3 c.c. + to 0.4 c.c. +	Slight improvement	
61	0.3, 0.4, 0.4	None	None	
63	0.3, 0.4, 0.4	None	None	
69	0.3, 0.4, 0.6	17 to 10	None	None	
19	0.3, 0.4	12 to 18	None	None	13 18 to 9
G. P. I. 13	0.3, 0.5	19 to 13	None	None	14 43 to 13
T. D. 14	0.3, 0.4	33 to 35	None	None	20 35 to 26
17	0.3, 0.5	90 to 88	None	None	20 88 to 17
C. S. 50	0.3, 0.5	22 to 28	None	None	23 28 to 20
T. D. 53	0.3, 0.5	16 to 20	None	None	18 20 to 11
54	0.3, 0.5	72 to 72	None	None	20 72 to 30
55	0.3, 0.5	17 to 17	None	None	16 17 to 11
56	0.3, 0.4	29 to 20	None	None	26 20 to 12
57	0.3, 0.5	14 to 8	None	None	
G. P. I. 56	0.3, 0.4	80 to 86	None	None	20 86 to 63
T. D. 46	0.4, 0.4	14 to 18	None	None	18 18 to 5
48	0.3, 0.4	37 to 36	None	None	16 36 to 16
44	0.3, 0.5	23 to 20	None	None	18 20 to 21
51	0.3, 0.4	32 to 20	None	None	18 20 to 9
65	0.3, 0.4	31 to 26	None	None	12 36 to 29
M. 70	0.3, 0.5	234 to 284	None	None	20 284 to 30
C. S. 58	0.4	100 to 100	None	None	18 100 to 19
M. 59	0.3	85 to 125	None	None	18 125 to 20
M. 42	0.2	2,500 to 2,500	None	None	15 2,800 to 7,300

* In this and in the following tables T. D. = tubes dorsales; C. S. = cerebrospinal syphilis; M. = syphilitic meningitis; G. P. I. = general paresis of the insane. The number represents the name of the case, each case appears by its own number throughout the paper.
 In reviews in the paper a single + means complete fixation and is an abbreviation for ++++.

little differential diagnostic importance. Treatment in all cases with high cell counts was followed by more rapid improvement in the symptoms and in the Wassermann reaction and a more rapid fall in the number of cells than in the cases with the low cell counts; from this we may infer that high cell counts represent early involvement of the tissues.

The foregoing inference seems to be evidenced by the fact that too frequent or too large doses of salvarsanized serum are immediately followed by an increase in the spinal fluid cell count, probably a result of irritation. In our experience the cell count in untreated cases has not varied, with the exception that in an occasional tabetic during a severe crisis of pain the cell count temporarily increased. To summarize, the effects of treatment on the intensity of the Wassermann reaction carried the greatest weight, and much reliance was placed on the spinal fluid cell count and considerable importance was put on a progressive, permanent improvement in major symptoms, such as severe pain, ataxia, incoordination, incontinence and abnormal mentality.

Other tests were applied to the spinal fluid at irregular intervals. These consisted of the trichloroacetic acid test for albumin, the magnesium sulphate and the Noguchi tests for globulin and the reduction test with Fehling's solution. The colloidal gold reaction was tried for a period of three months, but in our experience gave no added information, so it was discontinued.

The protocol given in Table 1 shows the effect of a few doses of intravenous salvarsan on the patients' symptoms and on the spinal fluid, as demonstrable by the Wassermann reaction and the cell count. Those patients who were later given intraspinal salvarsanized serum are also indicated and the effect of the first intraspinal treatment on the cell count is shown; the effect of this one treatment on the Wassermann reaction and on the symptoms will be mentioned in the discussion of the protocol.

The protocol given in Table 1 shows six cases in each of which the patient received six large doses of intravenous salvarsan. One patient, Case 52, was greatly improved in every way; the spinal fluid cell count decreased from 98 to 27, the spinal fluid Wassermann reaction was changed from 0.3 c.c.² positive to 1 c.c. negative and the symptomatic improvement, which was marked, is noted in the case report. Another patient, Case 71, evidenced a marked improvement in the spinal fluid Wassermann reaction, from 0.8 c.c. positive to 1.5 c.c. negative, and a drop in the cell count. This was an early case in which the patient had a rash and no other symptoms.

2. These figures throughout refer to the amount of spinal fluid used in the Wassermann test.

The other four patients evinced little or no improvement. In Case 1 the cell count dropped from 44 to 35 during the salvarsan treatments, but one week following the first intraspinal treatment with salvarsanized serum there was a more marked drop in the cell count, that is, from 35 to 7. In Case 22 there was slight temporary improvement in the symptoms only; the first intraspinal treatment produced a provocative reaction in the spinal fluid, and 1 c.c. was required before the intraspinal treatment gave complete fixation, whereas a week after the intraspinal treatment complete fixation was obtained from 0.5 c.c. The patient in Case 3 was somewhat relieved of pain, and ataxia was slightly improved; but the patient in Case 2 showed no demonstrable improvement whatever.

Therefore, of the six patients who each received six large intravenous doses of salvarsan, two evidenced marked improvement and four showed little or no improvement; two of these latter were given intraspinal salvarsanized serum with marked benefit (see Cases 22 and 1 in the case reports). The two markedly improved patients had very recent infections.

To each of five patients were given five large doses of intravenous salvarsan, and all but one showed slight improvement in one way or another. The patient in Case 6 showed a slight improvement in the spinal fluid, and the one in Case 63 showed a drop in the cell count and relief of pain and headache and some improvement in spasticity. The patient in Case 72 showed no improvement whatever, while the one in Case 7 was relieved of headache and dizziness. Patient 67 showed slight improvement in incontinence, and the cell count dropped from 15 to 7. Therefore in these five patients to each of whom was given five doses of salvarsan there was a slight improvement as indicated by the Wassermann reaction in one, improvement as shown in the cell count and in the symptoms in two, marked symptomatic improvement in a third, and no improvement at all in the fifth.

One of the two patients who received four doses of salvarsan each was much improved. This was a patient, Case 37, with syphilitic meningitis, whose primary infection occurred only nine months previous to this treatment. In this case all symptoms were relieved, the spinal fluid cell count dropped from 940 to 33, and the spinal fluid Wassermann reaction changed from 0.5 c.c. positive to 1 c.c. positive. The other patient of this group was not benefited in any way. Thus it is seen that in an early case much improvement may follow only four intravenous doses of salvarsan.

Twelve patients are represented as having received three doses of intravenous salvarsan; one patient, however, Case 52, is included in the first group of patients who received six doses and is repeated here in order to illustrate the improvement which followed only three doses

of salvarsan. This patient showed much improvement symptomatically and in the spinal fluid by a drop in the cell count from 98 to 60. Of the other eleven patients, only one, Case 61, showed any improvement in the Wassermann reaction; namely, a positive reaction with 0.3 c.c. became a positive with 0.4 c.c. Three patients showed a decrease in the cell count, Case 28 from 100 cells to 80, Case 47 from 80 cells to 21, and Case 69 from 17 cells to 10. Three other patients showed slight improvement in symptoms. In two patients the cell count increased. Eight patients who showed no improvement in any way from salvarsan alone were later given intraspinal salvarsanized serum, and the result of the first intraspinal treatment on the cell count is shown; namely, a big drop in every case; and in one patient, Case 45, a provocative Wassermann reaction was obtained in the spinal fluid. Case 23 should be especially noted as it was one of very severe syphilitic meningitis, with all its classical signs and symptoms, and the patient was unimproved by salvarsan and mercury, but great improvement both in the symptoms and in the cell count followed one intraspinal treatment (see case report). Therefore, much improvement may result from three doses of salvarsan, as shown by the patient in Case 52, and some improvement is shown in three others, 23, 49 and 61. The eight patients showing no improvement whatever following three doses of salvarsan, however, did show a marked drop in the cell count following one intraspinal treatment, and four of the eight showed some improvement in the symptoms; in one patient, Case 23, the symptoms were relieved, and in one a provocative reaction was obtained in the spinal fluid.

The remaining twenty cases in this protocol may be considered together, since seventeen patients received two doses of salvarsan and three only one dose. Naturally, little or no improvement in the symptoms or in the Wassermann reaction would be expected from so little treatment, and only a slight change would likewise be expected in the cell count. Nevertheless, the same should hold true for one intraspinal treatment. As a matter of fact, the cell count was reduced slightly in three cases, increased slightly in three and increased markedly in two others, following salvarsan. However, following the first intraspinal treatment, the cell count was reduced in all cases and in seven of these it was greatly reduced and in eleven of the cases it was reduced one half or more. Therefore, in this group of cases one can compare the effect of one or two doses of salvarsan with one intraspinal treatment, and in so doing one finds that the one intraspinal treatment caused a much greater reduction in the cell count than was caused by the salvarsan alone; this fact is conspicuously illustrated in Cases 42, 59, 58 and 70.

Summary of Protocol in Table 1: It seems fair to state that 3, 4, 5 or 6 injections of salvarsan at weekly intervals, occasionally produced great benefit in patients with central nervous system syphilis, such benefit being evidenced by improvement in the patients' symptoms, by the cells count and by the Wassermann reaction in the spinal fluid. Analysis of these three cases in which the patient showed great improvement reveals that they were recent infections, two of the patients having had their primary lesions less than a year previous to the nervous system involvement and the other her primary lesion five years' previously. It is further noted that maximum improvement was obtained by three and four injections of salvarsan in patients with recent infection. Offsetting these two early cases were two other very similar cases, both recent infections, in which the patients derived no improvement from three injections of salvarsan, together with intramuscular mercury, but these same patients did improve greatly in symptoms and there was a large reduction in the cell count following one intraspinal treatment. The other cases in the protocol were all of long-standing infections, so that they cannot be fairly compared with these recent cases, but these old cases do illustrate how slight the improvement may be following five or six injections of salvarsan. Furthermore, some of these patients with long-standing infections who did not improve under salvarsan showed a big drop in the cell count following the first intraspinal treatment. This drop was probably not a belated result from the salvarsan, since three patients who were given only one injection of salvarsan without improvement did show a big drop in the cell count a few days after one intraspinal treatment. Therefore, in all fairness it must be admitted that the protocol shows that some patients with long-standing nervous system syphilis improve remarkably following from three to six injections of salvarsan, whereas others do not improve; that long standing infections are very resistant to salvarsan alone; that patients with early and those with late infections who do not improve under from three to six injections of salvarsan do undergo a considerable improvement as shown by the cell count and some improvement in the symptoms following one intraspinal treatment; so that intraspinal salvarsanized serum in conjunction with intravenous salvarsan would seem to yield better results in all cases than intravenous salvarsan alone.

In the protocol given in Table 2 appear all cases of patients who were given three or four doses of both intravenous salvarsan and intraspinal salvarsanized serum, and for comparison with the previous protocol only the first three or four treatments are tabulated.

In the protocol in Table 2 are shown in fifteen cases only the first three injections of salvarsan, each followed by intraspinal salvarsanized serum, and in fifteen cases are shown the first four double treat-

ments. The amount of salvarsan and the amount of serum injected are presented, together with the spinal fluid cell count before and after each treatment, the change in the Wassermann reaction in the spinal fluid, and the change in the patients' symptoms after the third or fourth treatment, as the case may be.

In the last column much improvement is shown in all patients. All patients with headache, dizziness, vomiting, paresthesia, etc., were relieved of these; all twelve patients suffering pain, were relieved except one, and that one was improved; all seven patients with ataxia were improved, and one was relieved; the five patients with mental disturbances were all improved; incontinence was relieved and objective symptoms were improved by three or four combined treatments.

Improvement was shown by the Wassermann reaction in the spinal fluid in all but four of the twenty-nine cases. Although this improvement amounted to but 0.1 c.c. less positive, much change following so little treatment could not be expected.

The table shows in most cases a gradual drop in cell count following each treatment, and in all but three cases the cell count reached ten or less, and in thirteen cases a normal count was obtained, if we accept five cells as the upper limit of normal. The first treatment was followed by a slight rise in the cell count in one case, and by no change in two cases, but following the second treatment a big drop was obtained in all of these. Reference to the previous protocol, Table 1, shows that eight cases appear there in which the patients obtained no improvement from three to six injections of salvarsan. These same cases appear also in the protocol of Table 2, showing the patients to have improved in every way following three or four combined treatments. Likewise, in Table 1, several patients who showed no improvement following three injections of salvarsan present a record in Table 2 of improvement following three or four combined treatments.

Summary of Protocol in Table 2: It is evident that three or four injections of salvarsan and salvarsanized serum together were followed by much improvement in all patients; that pain, headache, dizziness, vomiting, paresthesia, etc., were relieved, that ataxia and mental disturbances became less severe, and that no patient became worse. There was a slight diminishing of the intensity of the positiveness of the Wassermann reaction in all but five cases. The cell count in all cases showed a marked decrease, in thirteen cases it was reduced to a normal of five and in only three cases did it not approach ten. The one patient, Case 15, who showed the least symptomatic improvement, evinced no change in the Wassermann reaction, and the cell count reached only 31. A comparison of this table with the preceding one shows better results in every way followed the combination treatment

TABLE 2.—EFFECT OF THREE OR FOUR DOSES OF INTRAVENOUS SALVARSAN AND INTRASPINAL SALVARSANIZED SERUM ON THE CELL COUNT,
THE WASSERMANN AND THE CLINICAL SYMPTOMS

Case Number	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Salvar., Gm.	Serum, C.c.	Cell Count	Change in Wassermann Reaction, C.c.	Clinical Improvement
T. D., 29	123	0.3	20	23	0.4	18	25	0.4	20	19	0.5+ to 0.8+	Pain and ataxia less
G. P. I., 21	166	0.3	20	14	0.4	20	16	0.4	0.05+ to 0.1+	Headache, paresthesia relieved
	115	0.3	14	99	0.4	22	30	0.5	18	19	0.05+ to 0.2+	Headache, aphasia, diplopia relieved
T. D., 15	108	0.4	16	...	0.4	18	...	0.5	20	31	None	Incontinence, ataxia less
	69	0.4	14	47	0.5	20	13	0.5	20	15	0.2+ to 0.3+	Pain relieved, ataxia less
C. S., 18	84	0.4	20	10	0.4	20	16	0.4	23	10	0.2+ to 0.3+	Mentality improved
G. P. I., 26	56	0.4	20	63	0.5	20	40	0.6	20	30	0.2+ to 0.3+	Pain relieved, mentality improved
T. D., 29	87	0.3	18	86	0.6	18	15	0.4	25	11	0.1+ to 0.2+	Ataxia, paresthesia relieved
	35	0.1	18	7	0.5	20	2	0.6	16	1	None	Incontinence relieved, ataxia less
G	32	0.3	20	20	0.4	20	20	0.5	18	10	0.2+ to 0.3+	Pain, paresthesia relieved
C. S., 45	14	0.6	16	5	0.6	18	4	0.5	25	...	1.0+ to 1.0—	Paresthesia relieved, mentality improved
T. D., 15	37	0.2	19	16	0.4	20	25	0.6	18	8	0.2+ to 0.3+	All symptoms relieved
	33	0.5	20	21	0.5	22	20	0.4	20	20	None	Symptoms relieved, ataxia less
	15	0.4	20	17	0.6	25	...	0.6	26	7	0.3+ to 0.6+	Tremor relieved, mentality improved
	60	0.4	14	33	0.4	22	15	0.4	26	10	0.1+ to 0.2+	Gastric symptoms relieved
G. P. I., 13	43	0.5	20	13	0.6	20	40	0.6	...	5	0.05+ to 0.2+	Pain, headache, dizziness relieved
	37	0.6	18	16	0.5	20	46	0.5	22	7	0.3+ to 0.4+	Pain, vomiting relieved
C. S., 10	47	0.6	16	25	0.6	18	23	0.5	20	16	0.2+ to 0.4+	Ataxia relieved, mentality improved
P. D., 14	75	0.4	20	26	0.5	20	20	0.5	25	16	0.1+ to 0.2+	Pain, vomiting relieved
	18	0.4	16	9	0.5	18	5	0.4	20	5	None	Pain, dizziness, depression relieved
C. S., 8	62	0.4	18	24	0.5	20	9	0.6	18	5	0.3+ to 0.4+	Headache, dizziness relieved
T. D., 9	75	0.4	20	20	0.5	22	8	0.5	20	7	0.3+ to 0.4+	Pain, paresthesia relieved
	71	0.4	20	9	0.6	20	10	0.6	15	9	0.2+ to 0.3+	Pain, paresthesia relieved
	16	0.5	18	10	0.5	20	5	0.4	16	2	None	Pain, paresthesia, dizziness relieved
C. S., 22	...	0.7	20	24	0.7	25	6	0.6	20	4	0.1+ to 0.3+	Diplopia relieved, mentality improved
P. D., 6	7	0.4	...	7	0.4	20	...	0.4	26	1	0.3+ to 0.3+	Pain relieved
	25	0.5	18	14	0.5	20	16	0.4	25	15	0.3+ to 0.5	Ataxia relieved
	34	0.4	0.4	20	9	0.5+ to 0.5+	Pain relieved
	1	...	0.4	0.1+ to 0.1+	Pain relieved

of intravenous salvarsan and intraspinal salvarsanized serum than followed salvarsan alone.

We now desired to determine the effect of intraspinal salvarsanized serum alone. For this method of treatment we selected cases with a negative Wassermann reaction in the blood serum, but with positive findings in the spinal fluid. The results appear in the protocol given in Table 3.

The protocol in Table 3 consists of twenty cases in which the patients were treated with intraspinal salvarsanized serum alone. For comparison with the preceding protocol only the first three or four intraspinal treatments and their results are tabulated. The Table shows the amount in cubic centimeters of salvarsanized serum given at each treatment, the cell count before and after each treatment, the resultant change in the Wassermann reaction, and the improvement in symptoms. The last two cases, 60 and 62, should be excluded when comparing this protocol with the former one, since both patients were given two intraspinal treatments with normal serum and one intraspinal treatment with salvarsanized serum.

The improvement in symptoms following three or four intraspinal treatments with salvarsanized serum was marked in all cases; those patients complaining of pain, headache, diplopia, numbness, etc., were relieved; those with ataxia were improved; and the three with signs and symptoms of meningitis were relieved.

The Wassermann reaction in three cases showed no change after three treatments and in two others it was negative before treatment. In thirteen cases the positiveness of the Wassermann reaction was diminished, this amounting to 0.1 c.c. in eight cases, to 0.2 c.c. or more in five others and in one case the reaction which was positive with 0.5 c.c. before treatment became negative with 1 c.c. after three treatments. (Compare this latter case with the patient in Case 52, in whom the same result was accomplished by three doses of intravenous salvarsan.) The ten cases starred ultimately became negative with 2 c.c. after more treatment.

The spinal fluid cell count diminished in all cases but one, and this one had only seven cells before treatment. In most cases the cell count diminished gradually, but the three cases with the high counts showed a rapid reduction. Eight cases had a normal cell count after three treatments, and in five others it had diminished to twelve or less. Case 27 illustrates the effect on the cell count of too frequent treatments, as following each of the first two treatments the cell count was diminished, but following the third treatment the count was increased by over 100 cells; however, the cells reached the previous low level after treatment was omitted for two weeks. Accompanying the increased cell count due to overtreatment in this latter case was a

TABLE 3.—EFFECT OF THREE OR FOUR DOSES OF INTRASPINAL SALVARSANIZED SERUM ALONE ON CELL COUNT.
WASSERMANN REACTION AND CLINICAL SYMPTOMS

Case Number	Cell Count	Salvarsanized Serum, C.c.	Cell Count	Salvarsanized Serum, C.c.	Cell Count	Salvarsanized Serum, C.c.	Cell Count	Change in Wassermann Reaction, C.c.	Clinical Improvement
T. D.	26	15 of 0.6	29	25 of 0.6	11	27 of 0.5	5	None*	Pains relieved
	27	14 of 0.4	100	27 of 0.5	37	20 of 0.1	165	0.4+ to 0.5+*	Pains relieved, ataxia less
	24	16 of 0.4	26	20 of 0.4	29	18 of 0.4	5	0.1+ to 0.2+	Pain, dizziness relieved, ataxia less
	25	15 of 0.4	3	20 of 0.4	3	25 of 0.6	0	None	Pain, dizziness, numbness relieved
	4	20 of 0.4	10	20 of 0.4	9	20 of 0.4	1	0.4+ to 0.5+*	Pain, headache, insomnia relieved
	28	20 of 0.4	18	20 of 0.4	40	18 of 0.6	27	0.2+ to 0.3+*	Pain relieved
	22	20 of 0.4	6	15 of 0.6	6	20 of 0.6	6	0.5+ to 0.6+	Pain relieved, ataxia less
	24	14 of 0.4	5	20 of 0.4	3	21 of 0.4	3	0.4+ to 0.6+	Gastric crises relieved temporarily
	27	15 of 0.4	3	20 of 0.4	3	20 of 0.4	1	0.6+ to 0.9+*	Pain, numbness relieved
	27	20 of 0.4	23	15 of 0.5	11	20 of 0.5	..	1.0 -	Pain, headache relieved
	1	15 of 0.4	13	20 of 0.6	7	25 of 0.5	..	1.0 -	Pain relieved, ataxia less
C. S.	17	15 of 0.4	20	20 of 0.5	9	20 of 0.5	..	0.3+ to 0.4+	Headache relieved
	1	20 of 0.5	35	20 of 0.5	20	20 of 0.5	12	None	Headache, diplopia relieved
M.	2	20 of 0.4	272	20 of 0.5	100	25 of 0.6	16	0.1+ to 0.2+*	Headache, diplopia, positive Kernig's, stiff neck relieved
	1	15 of 0.4	7,000	15 of 0.4	2,500	20 of 0.6	125	0.05 to 0.2+*	Ophthalmos., positive Kernig's, stiff neck relieved
F. P.	4	16 of 0.6	9	20 of 0.6	15	25 of 0.6	3	0.5 to 0.8+	Pain relieved, incontinence less
	2	15 of 0.4	16	15 of 0.6	12	20 of 0.6	10	None	Pain relieved
	2	16 of 0.5	11	20 of 0.5	11	20 of 0.5	5	0.6+ to 0.7+	Pain relieved
G. P.	20	20 normal	67	20 normal	94	15 of 0.4	53	None	
	7	20 normal	8	20 normal	10	20 of 0.4	123	1.0—	Severe pain for four days

* These cases ultimately gave a negative Wassermann reaction in the spinal fluid with 1 or 2 cubic centimeters following more treatment.

slight remission in the symptomatic progress, and the spinal fluid showed the presence of red blood cells; these same findings resulted a second time in this same case and also occurred in two other cases following a larger number of treatments. In Case 60, which was one of general paresis of the insane with a positive blood reaction, the patient was given two intraspinal treatments with normal syphilitic serum without producing any effect on the cell count; but following one intraspinal treatment with salvarsanized serum the cell count diminished one half. In Case 62, which was not a case of syphilis and had negative reactions in both blood and spinal fluid and a cell count of eight, the patient was given two intraspinal treatments with syphilitic serum without producing any effect on the cell count; however, following one intraspinal treatment with salvarsanized serum, the cell count increased to 123, many red blood cells were present, and the patient complained of severe pain for four days. These two latter cases serve as controls, in that syphilitic serum, not salvarsanized, had no effect on the cell count, whereas salvarsanized syphilitic serum produced beneficial effects, shown by a big drop in the cell count in the case of the syphilitic; but in the case of the nonsyphilitic the salvarsanized syphilitic serum produced ill effects, evidenced by a greatly increased cell count, the presence of red blood cells in the spinal fluid and severe pain. Therefore, one must admit that there is something present in salvarsanized serum that is absent in syphilitic serum, and this something produced beneficial effects in the case of the syphilitic, and ill effects in the case of the nonsyphilitic.

In summarizing this protocol we think it shows the advantage and value of intraspinal salvarsanized serum alone, and that it is further proof that intraspinal salvarsanized serum is a great adjunct to intravenous salvarsan. In certain cases in which intravenous salvarsan is contraindicated intraspinal salvarsanized serum may be given with safety and with possible success; the patient in Case 64, who had edema, and albumen and casts in the urine following intravenous salvarsan, was later given intraspinal salvarsanized serum alone and rapid improvement followed.

So far in this paper we have attempted to show the results following a limited number of treatments which were given by the three different methods. By so doing we have attempted to bring out the value of each method, and to show that when satisfactory results do not follow one method, for instance salvarsan alone, another method, the combination of salvarsan with intraspinal salvarsanized serum, may yield rapid results, thus rendering the treatment of central nervous system syphilis less discouraging. The remainder of the paper is concerned with the entire treatment and its results in each case, and with the condition of the patient after an interval without any treatment.

The patients treated with salvarsan alone are quite thoroughly discussed in connection with the protocol given in Table 1, so that only a few words are necessary before dismissing this method of treatment. Cases M. 37, C. S. 63, C. S. 71 and C. S. 52 were distinctly benefited by salvarsan alone. In Case M. 37, one of meningitis following the primary lesion by only nine months, the patient, whose serum reaction was positive and whose spinal fluid contained 940 cells and was positive with 0.5 c.c., was relieved of all symptoms and signs of meningitis, and the spinal fluid cell count was reduced to 33 and the Wassermann reaction to 1 c.c. positive by four doses of salvarsan. Case C. S. 52 is the record of another patient with very recent infection who was greatly improved by six doses of salvarsan; the spinal fluid cell count dropped from 90 to 20, and the Wassermann reaction was changed from 0.3 c.c. positive to 1 c.c. negative. The record in Case C. S. 71 is that of a patient whose only symptom was a late rash, which was preceded by a primary lesion by less than four years. He was given six injections of salvarsan, following which the spinal fluid cell count became normal and Wassermann reaction became negative with 1.5 c.c. In Case C. S. 63 the patient complained of pain, headache and spasticity of the legs. He had had a primary lesion four years before. Following five doses of salvarsan there was no change in the spinal fluid Wassermann reaction, although the cell count became normal and the pain and headache were relieved. Three more doses of salvarsan, a total of eight, changed the Wassermann reaction in the spinal fluid from 0.1 c.c. to 0.3 c.c. positive; and four more injections, a total of twelve, changed it from 0.3 c.c. positive to 0.4 c.c. positive. Therefore, in these four patients, all with recent infections, satisfactory results followed salvarsan alone.

Nine other patients, all with much older infections than the above four, were treated with as many or more injections of salvarsan than were the above four patients, and little or no benefit resulted. The patients with the records given in Cases T. D. 1, 2, 4, and 22 were given respectively six, six, nine, and twelve injections of salvarsan without any benefit in the symptoms or in the laboratory findings; however, in all of these cases satisfactory results followed when intraspinal salvarsanized serum was used either alone or in conjunction with intravenous salvarsan. The patients in Cases T. D. 3, 6, and 67 were somewhat improved symptomatically following six intravenous doses of salvarsan, although there was practically no change in the laboratory findings. In case 7 the patient was relieved of symptoms following five doses of salvarsan, but no improvement was noted in the laboratory findings. Case C. S. 72 is the record of a patient who derived no benefit in any way from five doses of salvarsan, but who intraspinal salvarsanized serum was given in conjunction with four

venous salvarsan, the spinal fluid cell count quickly fell, the Wassermann reaction became more faintly positive, and there was an improvement in the patient's sensory symptoms.

The following summary seems justifiable from this series of thirteen cases in which the patients were treated with salvarsan alone. Patients with recent cases of syphilitic meningitis and cerebrospinal syphilis may be greatly benefited or even relieved by salvarsan alone. Those with older infections, such as tabes dorsalis and cerebrospinal syphilis, derive little or no benefit from salvarsan alone as a rule; however, an occasional case may be benefited or relieved symptomatically only.

The protocol outlined in Table 4 gives diagrammatically a fair idea of the treatment and the results obtained in the patients treated with intravenous salvarsan or diarsenol,¹ and with intraspinal salvarsanized or diarsenolized serum. The patients in the thirty cases comprising the protocol received a total of 215 intravenous and 188 intraspinal treatments. Ten other patients belong to this group, but their cases are not shown, as each was given, for various reasons, only two double treatments; most of these cases appear in other parts of this paper. In twenty-one cases the diagnosis was tabes dorsalis, in three it was cerebrospinal syphilis, and in six it was general paresis of the insane. The results of treatment will be considered as immediate and final. By immediate results is meant symptomatic improvement, and a decrease in the positiveness of the Wassermann reaction and a decrease in the spinal fluid cell count. By final results is meant whether improvement was only temporary or permanent and whether the patient, who was previously incapacitated, was benefited enough to be able to resume work, or in other words, was there any economic value derived from treatment.

. As an immediate result from treatment, pain, the most frequent symptom, which was present in nineteen cases, was relieved, as was also headache, dizziness, paresthesia, anesthesia, vomiting, indigestion, diplopia and incontinence. Those patients with such mental symptoms as irritableness, aphasia, impaired memory and depression were all improved, and in many these symptoms were so subdued as to be rendered unnoticeable. Ataxia, which was present in eighteen cases, was relieved in eight, markedly reduced in five and much reduced in five. The only physical sign that was changed was that in only one case a positive Romberg became negative.

The Wassermann reaction in the spinal fluid was diminished in intensity in twenty-five of the thirty cases. In eight of these the improvement was only 0.1 c.c., in ten it was from 0.3 c.c. to 0.5 c.c. diminished, and in five there was a greater improvement, the reaction becoming negative with 1 c.c. The amount of treatment cannot be

TABLE 4.—EFFECT OF ~~INTRAVENOUS~~ SALVARSAN WITH INTRASPINAL SALVARSANIZED SERUM

Case Number	Number of Treatments		Change in Wassermann Reaction, C.e.	Clinical Improvement	Interval With-out Treatment, Months	Remarks
	Intra-venous Salvar.	Intra-spinal Serum				
T. D. 5	4	1	0.2+ to 0.3+	Pain, diplopia relieved; ataxia less.....	27	No return of symptoms
C. S. 1	23	21	0.2+ to 0.6+	Pain, incontinence relieved; ataxia relieved tempor.	20	Relapse in ataxia
T. D. 6	8	5	0.2+ to 1.0—	Pain, ataxia, incontinence, paresthesia relieved.....	8	No return of symptoms
9	4	1	0.2+ to 0.3+	Pain, paresthesia relieved.....	24	No return of symptoms
15	1	3	None	Pain, incontinence relieved; ataxia less.....	19	No return of symptoms; ataxia less
16	3	3	None	Pain, ataxia relieved; Romberg became negative....	24	No return of symptoms
17	7	6	0.2+ to 0.4+	Pain, incoordination, anesthesia relieved.....	12	No return of symptoms; is working
C. S. 8	3	3	0.3+ to 0.4+	Headache, dizziness relieved; memory improved.....	25	No return of symptoms; is working
G. P. L. 10	7	5	0.2+ to 0.5+	Ataxia relieved, aphasia less, memory improved.....	14	No return of symptoms; is working
11	9	9	0.05+ to 0.1+	Ataxia, headache, diplopia relieved; memory improv.	18	No return of symptoms; is working
21	3	3	0.05+ to 0.1+	Headache, paresthesia relieved; memory improved....	4	Died of cerebral hemorrhage
14	9	10	0.1+ to 0.1+	Pain, ataxia relieved.....	10	No return of symptoms; is working
46	7	4	0.1+ to 0.2+	Pain, diplopia relieved.....	6	No return of symptoms; is working
44	3	4	None	Headache, vomiting, ataxia relieved.....	6	No return of symptoms; is working
C. S. 17	3	3	1.0+ to 1.0—	Pain, ataxia relieved; mentality improved... ..	6	No return of symptoms; is working
G. P. L. 19	4	4	None	Pain relieved, mentality improved.....	9	Mental relapse
17	17	17	0.05+ to 0.1+	Pain, headache, dizziness, deafness relieved.....	3	One attack unconsciousness
43	6	7	0.1+ to 0.2+	Pain, ataxia, dizziness, indigestion relieved.....	8	No return of symptoms; is working
9	6	6	0.5+ to 1.0—	Pain relieved, ataxia greatly lessened.....	4	No return of symptoms; is working
G. P. L. 18	9	6	0.2+ to 0.4+	Symptoms relieved	3*	Died of pneumonia
C. D. 19	6	5	None	Pain, dizziness, depression, gastric symptoms relieved.	1*	Died of pneumonia
1	7	1	0.5+ to 0.4+	Pain, vomiting relieved.....	1*	Died of pneumonia
47	7	7	0.1+ to 0.7+	Pain, indigestion relieved.....	2	No return of symptoms; is working
49	9	9	0.5+ to 1.0—	Paresthesia, weakness relieved; ataxia greatly lessened	1	No return of symptoms; is working
41	7	7	0.1+ to 0.6—	Headache, numbness relieved; ataxia greatly lessened	2	No return of symptoms
1	1	1	0.1+ to 0.4	Headache, dizziness, ataxia relieved.....	7	No return of symptoms; is working
19	5	5	0.5+ to 0.7+	Pain, paresthesia relieved; ataxia lessened....	3	No return of symptoms
20	4	4	0.4+ to 0.5+	Pain, incontinence relieved; ataxia lessened..	4	Because of edema, albumin, casts, salivary gland omitted
21	5	4	0.4+ to 0.7—	Pain, gastric symptoms, ataxia lessened.....	7	No return of symptoms

correlated with the change in the Wassermann reaction. In one case twelve treatments changed the reaction from 0.1 c.c. to 0.4 c.c. positive, while in another case nine treatments changed the reaction from 0.3 c.c. positive to 1 c.c. negative. Many other similar comparisons may be drawn from the above protocol. The blood serum Wassermann reaction became negative in only one case.

No mention is made in the protocol of the effect of treatment on the spinal fluid cell count, as this has been mentioned earlier in the paper, where it was shown that four double treatments reduced the cell count to normal in nearly every case. No parallel can be drawn between the improvement in the cell count and in the Wassermann reaction. Symptomatic sensory improvement parallels fairly closely the diminishing of the cell count, as both occur during the early treatments, and after three or four treatments the cell count is usually at or near normal and sensory symptoms are usually relieved.

As a final result from treatment, thirteen patients out of fifteen previously incapacitated were restored in their economic value; they became able to work and did work. Two others who were unable to walk were improved to such an extent as to be able to get around with the aid of a cane. Four patients relapsed: one patient with tabes had a relapse in ataxia while under treatment, two with general paresis of the insane had mental relapses, one relapse being only slight and temporary; one patient with cerebrospinal syphilis had a relapse of weakness probably of cerebral origin. Four patients have died: three of these died of pneumonia one month after treatment, and the fourth, with a blood pressure of 240 mm. of mercury, died four months later of cerebral hemorrhage. The length of time which has elapsed since treatment was stopped has not been long in many cases. Reference to the protocol shows that in four cases a period of two years has elapsed, in three others eighteen months or more, in two others one year or more, and in eight others a period of six months or more has elapsed without untoward symptoms. The best and most permanent results were obtained in the cases of tabes; two of the six patients with general paresis were restored to working capacity and have shown no return of symptoms for fourteen and seventeen months, respectively; two of the three patients with cerebrospinal syphilis have been free from symptoms for six and twenty-five months respectively, one of these having been previously unable to work.

The protocol in Table 5 consists of seventeen cases in which the patients were treated with salvarsanized serum intraspinally and nothing else. Tabes dorsalis was the diagnosis in thirteen cases, syphilitic meningitis in two cases and cerebrospinal syphilis in two cases. The number of treatments which each patient received, the improvement in the symptoms and in the Wassermann reaction in the spinal fluid,

TABLE 5.—EFFECT OF INTRASPINAL SALVARSANIZED SERUM ALONE ON THE WASSERMANN REACTION AND ON CLINICAL SYMPTOMS

Patient	No. of Intra-spinal Serum Treat-ments	Change in Wassermann Reaction, C.c.	Clinical Improvement	Inter-val Since Treat-ment, Months	Remarks
T. D.	4	0.1+ to 2.0—	Pain, headache, insomnia, depression relieved.....	12	No return of symptoms; is working*
C. S.	13	0.3+ to 0.7+	Headache, anesthesia relieved; sight slightly improved.....	24	Occasional headache; is working
M.	23	0.1+ to 1.0—	Symptoms and signs of meningitis relieved.....	1	No return of symptoms; is working
T. D.	9	0.1+ to 1.0—	Gastric crises relieved.....	12	No return of symptoms
	10	None	Pain, dizziness, incontinence relieved; ataxia less.....	8	No return of symptoms; is working
	10	0.2+ to 1.0—	Pain relieved, sight improved, ataxia less.....	13	No return of symptoms; is working
	22	0.1+ to 2.0—	Pain, dizziness relieved, ataxia less.....	6	No return of symptoms; is working
	3	1.0—	Pain relieved, sight greatly improved, ataxia much less.....	11	No return of symptoms
	3	1.0—	Pain, headache, insomnia relieved.....	13	No return of symptoms; is working
	7	0.5+ to 1.0—	Pain, numbness relieved; ataxia less.....	1	No return of symptoms
	11	0.1+ to 0.4+	Pain, dizziness relieved; ataxia less.....	1	No return of symptoms
C. S.	5	None	Symptoms relieved	12	No return of symptoms; is working
T. D.	8	0.3+ to 1.0	Pain, vomiting relieved; ataxia less.....	6	No return of symptoms
M.	1	0.05+ to 0.0	Symptoms and signs of meningitis relieved.....	9	No return of symptoms; is working
T. D.	5	0.7+ to 0.00	Pain relieved, incontinence less.....	2	No return of symptoms
	4	0.1+ to 0.5+	Pain relieved	2	No return of symptoms
	9	0.5+ to 0.00	Pain, ataxia, numbness relieved.....	2	Slight relapse in ataxia, improving

* Patient was too feeble and this patient was unable to work.

the interval since treatment was omitted and the present condition of the patients are all indicated in the protocol. This protocol is almost an exact reproduction of the previous protocol as to temporary and permanent improvement, the differences being that the former illustrated cases with a positive serum reaction and positive spinal fluid findings, in which the patients were treated with salvarsan and salvarsanized serum, whereas, the latter protocol illustrates cases, with only positive spinal fluid findings, in which the patients were treated with only salvarsanized serum; furthermore in the latter group the Wassermann reaction became negative in more cases.

As an immediate result, pain, headache, dizziness, numbness, etc., were relieved; eye-sight was definitely improved in two patients, one of the two patients having incontinence was relieved and one improved. The one patient with gastric crises was practically relieved, whereas salvarsan had given no relief. A very noticeable improvement followed in the seven patients showing ataxia; one patient who showed no improvement following six treatments of salvarsan was relieved by the same number of serum treatments; of the other six ataxia patients four were unable to walk about the house previous to treatment, but these improved rapidly under treatment. The most striking improvement followed in the two patients with meningitis. One, a child, whose spinal fluid showed 9,800 cells and a positive reaction with 0.05 c.c., with stiff neck, opisthotonos and double Kernig, was relieved of signs and symptoms by three intraspinal treatments, and the cell count dropped from 9,800 to 126. The other patient, whose spinal fluid showed 550 cells and a positive reaction with 0.1 c.c., with stiff neck, double Kernig, and internal strabismus, was relieved of the signs and symptoms by two intraspinal treatments, and the cell count dropped from 550 to 100; the latter case had been given intensive antisymphilitic treatment with salvarsan, mercury, and potassium iodid without relief. Both of these cases ultimately gave negative reactions in the spinal fluid and had a normal cell count (see case reports). Three patients reacted too severely to weekly treatments, but this was overcome by two week intervals.

The Wassermann reaction showed no change following treatment in two cases and in two others it was negative before treatment. In one case a provocative reaction was obtained in the spinal fluid following one intraspinal treatment. The spinal fluid became negative with 1 c.c. in eight cases; in three of these 2 c.c. were tested and found to be negative, as was also the globulin test negative. Two cases showed a decrease in the positiveness amounting to 0.3 c.c., two others 0.4 c.c., and one 0.5 c.c. Therefore in this protocol more cases became negative, and in those which did not become negative, a greater change took place than did in the cases of the previous protocol. The cases of two

patients are of particular interest, in that the serum repeatedly gave a negative reaction while they were being treated intraspinally; but about the time the spinal fluid became negative the serum became positive, and much salvarsan was required to make it negative again.

As the spinal fluid cell count has already been referred to, suffice it to mention that the cell count rapidly decreased and paralleled closely the sensory improvement.

Some permanent results might be mentioned. Nine patients previously unable to work were so much improved by treatment that all have been working since treatment was omitted. One patient had a return of headache after eight months and two had a slight relapse in ataxia, not enough, however, to incapacitate them, and the relapse was only temporary and immediately followed treatment. Seven patients have been observed for twelve months or more since treatment was stopped, and there has been no retrogression in any of them; four others have gone six months or more without untoward symptoms.

Since several of these patients showed no improvement following the use of salvarsan, but improved rapidly while being treated with salvarsanized serum intraspinally alone, it would seem that this class of patients require only the latter form of treatment. Furthermore, there must be some value in salvarsanized serum injected intraspinally.

Summary: Seventy-five patients with central nervous system syphilis were treated with 450 intraspinal injections of salvarsanized serum and with 350 intravenous injections of salvarsan. At first only salvarsan was used, and a few patients improved rapidly. However, in many cases little or no improvement followed from three to six injections, so these patients were then given intraspinal salvarsanized serum in conjunction with the salvarsan, and they improved rapidly under the combined treatment (Swift-Ellis method). As the intraspinal treatment seemed to reinforce the salvarsan, we desired to determine what results would follow the intraspinal method alone. For this method we selected patients with a negative Wassermann reaction in the serum and with positive findings in the spinal fluid. The results from this method closely paralleled those from the double method. Therefore, the following rule has been adopted at this hospital: Patients are first treated with intravenous salvarsan. If satisfactory results do not follow three or four such treatments, they are then given intraspinal salvarsanized serum in conjunction with intravenous salvarsan. Those who have a negative reaction in the serum are given only intraspinal salvarsanized serum. The foregoing scheme is the basis of this paper.

The first part of this paper consists of three protocols which are followed in each case by a discussion. The first protocol consists of cases in which the patients were treated with from three to six injections of salvarsan alone; the second protocol is the record of patient

treated with three or four injections of intravenous salvarsan and intraspinal salvarsanized serum together, and the third protocol shows the record of those treated with three or four intraspinal injections of salvarsanized serum alone. The purpose of this part of the paper is to compare the results following a similar number of treatments given by the three different methods. By this comparison we find that the double (Swift-Ellis) method gave more rapid and more satisfactory results than was given by salvarsan alone, and furthermore, that the intraspinal salvarsanized serum alone gave rapid and satisfactory results. These results were evidenced by improvement in the patient's symptoms, by a drop in the cell count and by a decrease in positiveness of the Wassermann reaction in the spinal fluid.

The latter part of the paper deals with the total treatment given to each patient by the three methods. To thirteen patients were given five or more intravenous injections of salvarsan alone. Four of these patients, three with cerebrospinal syphilis and one with syphilitic meningitis, had very recent infections and were relieved of their symptoms. The spinal fluid cell count was reduced to normal in three cases, and the Wassermann reaction became negative with 1 c.c. in three cases. The remaining nine patients had older infections and they showed little or no improvement in their symptoms and no improvement in the spinal fluid findings.

To thirty patients were given three or more double (Swift-Ellis) treatments, and marked improvement followed in each case. Thirteen patients who were previously incapacitated were restored to working capacity; of eighteen with ataxia, eight were relieved, five were markedly improved and five more were much improved. Twenty-five patients showed improvement in the spinal fluid Wassermann reaction; in ten cases this amounted to from 0.3 c.c. to 0.5 c.c., and in five other cases the reaction became negative with 1 c.c. The spinal fluid cell count became five or less in twenty-five cases. In four cases a period of two years has elapsed since treatment without any return of symptoms, in three others a period of eighteen months and in eight others six months or more. Four patients have shown some form of relapse. One with tabes had a relapse in ataxia, two with general paresis of the insane had a temporary relapse in mentality, while one with cerebrospinal syphilis developed a weakness in the legs probably of cerebral origin.

Seventeen patients were treated intraspinally with salvarsanized serum alone, and all were markedly improved or relieved symptomatically. Nine who were previously unable to work were restored to working capacity. Of the seven patients with ataxia, four previously unable to walk at all, became able to work, and in the other three, in whom the ataxia was not so marked, there is great improvement. The

Wassermann reaction in the spinal fluid became negative with 1 c.c. or 2 c.c. in eight cases, and in five others it was improved from 0.3 c.c. to 0.5 c.c. The spinal fluid cell count became normal in nearly every case. In Cases 23 and 42, both syphilitic meningitis, the patients were relieved in every way. Seven patients have been observed twelve months since treatment was stopped, and four others for six months or more, and they show no return of symptoms. One patient with cerebrospinal syphilis had a return of headache after eight months, and two with tabes had a slight relapse in ataxia, which rapidly cleared up immediately following a treatment.

In one patient a provocative Wassermann reaction occurred in the spinal fluid following the administration of salvarsan, and in two cases a provocative reaction occurred in the spinal fluid following intraspinal treatment. Two patients with repeatedly negative reactions in the serum while under intraspinal treatment developed a positive reaction in the serum about the time the spinal fluid reaction became negative with 1 c.c.

Improvement in symptoms following treatment seemed to parallel fairly closely the drop in the cell count, and those patients with high cell count seemed to improve symptomatically more rapidly and the cell count dropped more rapidly than occurred in those cases with low cell count. The only physical sign which was changed in these cases was that a positive Romberg in one case became negative. More benefit seemed to follow moderate after-treatment reactions than when no reaction occurred. Severe reactions are undesirable and may be avoided by less frequent treatments. In this series of cases no fatal or disturbing results followed treatment.

In this series of cases the total number of cells in the spinal fluid did not vary as a rule. In a few cases of tabes, during severe crises of pain, and in cases immediately following too frequent and too large intraspinal injections of salvarsanized serum, the cell count temporarily increased. Since the cell count has become normal, the patients in Cases 1, 4, 6, 11, 13, 14, 26, 33 and 34 have received lumbar puncture repeatedly for over a year, and those in Cases 23, 25, 27 and 42 for over six months and no variation outside of two or three cells was found in a single instance. Many other patients received lumbar puncture at longer intervals since treatment was stopped and no variation in the cell count was found.

CONCLUSIONS

Patients with recent syphilitic meningitis and cerebrospinal syphilis may be relieved symptomatically by intravenous salvarsan; the spinal fluid Wassermann reaction may become negative with 1 c.c. and the cell count may become normal. Patients with long-standing

cerebrospinal syphilis and tabes may be benefited symptomatically following salvarsan, but little or no change occurs in the spinal fluid findings.

Patients with recent and those with late syphilitic meningitis, cerebrospinal syphilis, tabes and general paresis of the insane are markedly improved following the combination of intravenous salvarsan and intraspinal salvarsanized serum (Swift-Ellis method), and those who fail to improve under salvarsan alone do improve both in symptoms and in spinal fluid findings following this double treatment.

That intraspinal salvarsanized serum greatly benefits patients with central nervous system syphilis is shown by the fact that those with negative serum reactions and with positive spinal fluid findings are symptomatically relieved by this treatment. In many patients the spinal fluid Wassermann reaction becomes negative with 1 c.c., the cell count becomes normal and a negative (Noguchi) globulin test is obtained following sufficient treatment with salvarsanized serum intraspinally without other medication.

CASE REPORTS

TREATMENT WITH SALVARSAN AND INTRASPINAL SALVARSANIZED SERUM

CASE 1.—A man, aged 55, was admitted to the hospital April 10, 1913. A diagnosis of cerebrospinal syphilis was made. Seven years before he had had a chancre followed by a rash. He had had a temporary paralysis of his left leg and the left side of his face, with a marked speech defect one year after his original infection. For two years he had had pains in his left leg and marked ataxia and for one year he had had incontinence of urine and feces and loss of sexual power.

Physical examination showed irregular pupils, which reacted poorly to light. His deep reflexes were exaggerated. The patellar reflex was more active on the right than on the left. There was a positive Babinski and ankle clonus on each side. He walked with a spastic gait and there was marked swaying in the Romberg position. There was some incoordination of the movements of his feet and hands. Over his trunk and face there were irregularly distributed areas of anesthesia for touch. There was a left-sided facial paralysis.

The Wassermann reaction in his blood serum was negative. His spinal fluid showed a cell count of 42 per c.mm. and gave a positive Wassermann reaction with 0.2 c.c. of fluid.

He was given fifteen doses of 0.9 gm. neosalvarsan and thirteen doses of 0.4 gm. salvarsan and twenty-four intraspinal treatments with salvarsanized serum. After the first six doses of neosalvarsan there was no improvement. The first four double treatments relieved the incontinence of urine and feces and the pain and ataxia were improved. At the end of this time he was left without any treatment for two months and during this interval he became more ataxic. During the remaining treatments he continued to get more ataxic until he was able to walk only with a cane. The Wassermann reaction in his spinal fluid changed from positive with 0.2 c.c. to positive with 0.6 c.c. The cell count became normal and has remained so.

Treatment was discontinued twenty months ago. During this interval he has been free from all symptoms except ataxia and this seems to be slowly improving.

CASE 5.—A man, aged 45, was admitted to the hospital Aug. 28, 1913. A diagnosis of tabes dorsalis was made. He had a chancre thirty years before and for the previous five years he had had pains and numbness in his legs and a girdle sensation. For the same length of time he had had attacks of dizziness, which often caused him to fall. For seven months he had had incontinence of urine, failing vision, diplopia and paresthesia over his back. Three months before entrance to the hospital he had developed a Charcot knee.

Physical examination showed unequal pupils, which did not react to light. The deep reflexes of the legs were absent. There was incoordination in the movements of his arms and legs. He could not walk or stand alone.

The Wassermann reaction in his blood serum was negative. The spinal fluid gave a positive Wassermann reaction with 0.2 c.c. and showed a cell count of 26 per c.mm. He was given four doses of neosalvarsan and four doses of salvarsanized serum intraspinally. The treatment relieved his pains and paresthesia, and his diplopia disappeared. The cell count in his spinal fluid became normal and the Wassermann reaction changed from positive with 0.2 c.c. to positive with 0.3 c.c. Twenty-seven months have elapsed since the last treatment and there has been no return of symptoms. At the present time he can walk alone without difficulty except when turning quickly.

CASE 6.—A man, aged 43, entered the hospital Feb. 26, 1914. A diagnosis of tabes dorsalis was made. Twenty years before he had had a chancre which was followed by a rash. He had taken mercury by mouth for eight months and potassium iodid for several years. Five years before he had had several bad falls. Shortly afterward he had noticed that he could not walk straight and that his feet had become numb. For three years he had had shooting pains in his legs. During the previous year he had lost his sexual power and had felt weak and tired.

Physical examination showed a positive Romberg test, absent deep reflexes in his legs and Argyll Robertson pupils.

The Wassermann reaction in the blood serum and in the spinal fluid was positive, with a spinal fluid cell count of 32 per c.mm.

He was given eight doses of salvarsan and five intraspinal treatments with salvarsanized serum. This amount of treatment relieved all of his symptoms and he was able to play tennis and golf. The cell count in his spinal fluid became normal and the Wassermann reaction changed from positive with 0.2 c.c. to negative with 1 c.c. After an interval of six months he was given six additional doses of salvarsan, because his blood serum continued to give a positive Wassermann reaction. Another six months have now elapsed without treatment and the patient is feeling perfectly well.

CASE 8.—A man, aged 42, entered the hospital Nov. 20, 1913. A diagnosis of cerebrospinal syphilis was made. He had had a chancre fourteen years before, which had been followed by a rash and sore throat. He had been treated for three years with mercury by mouth and injection. Two and a half years before he had been given one dose of salvarsan. During the year previous to entrance he had had very severe headaches, dizziness, difficulty in speech, failing memory and a temporary paralysis of his left face and arm. He had been unable to work for the previous six months.

Physical examination showed a poor reaction of his pupils to light, hyperactive reflexes, ataxia of his left arm and poor memory.

The Wassermann reaction was positive in both blood serum and spinal fluid with a spinal fluid cell count of 63 per c.mm.

He was given three doses of salvarsan and three doses of salvarsanized serum intraspinally. This amount of treatment relieved his headaches, dizziness and irritability. The spinal fluid cell count was reduced from 63 to 6 per c.mm. The Wassermann reaction in the spinal fluid was changed from positive with 0.3 c.c. to positive with 0.4 c.c. Twenty-five months after the last treatment he was free from symptoms and had gained thirty pounds in weight.

CASE 9.—A woman, aged 45, entered the hospital Dec. 16, 1913. A diagnosis of tabes dorsalis was made. She had had pains in the legs for several years, but during the previous few weeks the pains had become more severe and had involved the arms and body. She had had some mental disturbance, particularly depression, for several weeks.

Physical examination showed Argyll Robertson pupils, hyperactive reflexes and disturbed sensation about the waist.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a cell count in the latter of 25 per c.mm.

She was given four doses of neosalvarsan and four doses of salvarsanized serum intraspinally. At the end of six weeks all pain and hyperesthesia were relieved. Mentally she seemed normal. The spinal fluid cell count was reduced to 2 per c.mm. and the Wassermann reaction was changed so that 0.3 c.c. was required to give a positive test, while at the first observation only 0.2 c.c. was necessary. She was treated last twenty-four months ago and during that time she has had no return of symptoms.

CASE 10.—A man, aged 50, entered the hospital Sept. 23, 1914. A diagnosis of general paresis of the insane was made. The patient had had a chancre twelve years before and had been treated for eighteen months with potassium iodid and mercury by mouth. For a year previous to entrance he had been irritable, restless, inattentive and easily fatigued. Three months previously he had lost his memory for a week and had developed a facial paralysis. Within the previous few weeks he had noticed tremor of his hands, ataxia, periods of mental depression, trouble with his speech and writing.

Physical examination showed Argyll Robertson pupils, exaggerated and unequal knee jerks, tremor of the tongue and facial muscles, poor memory, slurring speech, and handwriting characteristic of general paresis.

The Wassermann reaction was positive in both blood serum and spinal fluid. The spinal fluid cell count was 47 per c.mm.

Seven doses of salvarsan and five intraspinal treatments of salvarsanized serum were given to this patient. At the end of two months there was great improvement in his memory. He was not depressed or irritable. There was no ataxia and he had returned to work. The Wassermann reaction in his spinal fluid was changed from positive with 0.2 c.c. to positive with 0.5 c.c. The cell count was reduced from 47 to 5 per c.mm. The patient was heard from fourteen months after leaving the hospital; at this time he was feeling perfectly well and had no return of his former symptoms.

CASE 11.—A man, aged 62, entered the hospital Feb. 26, 1914. A diagnosis of general paresis of the insane was made. Twelve years before he had had a chancre. For the previous year he had been run down and tired, had had attacks of vomiting and one period of aphasia. He stated that he had given up work because of fatigue, loss of memory, inability to concentrate, diplopia and disturbance in gait.

Physical examination showed that his pupils were unequal and irregular, but reacted to light. All reflexes were hyperactive. There was a positive Romberg test and some tremor of the tongue and muscles of the face. The Wassermann reaction in the blood serum was positive and it was also positive in the spinal fluid with 0.05 c.c. There was a spinal fluid cell count of 145 per c.mm.

He was given nine doses of salvarsan and nine treatments with salvarsanized serum intraspinally. The first few treatments relieved the diplopia, aphasia, abnormal sensations and numbness. Under further treatment his memory gradually improved until it seemed about normal, the tremor of his facial muscles decreased somewhat and he became able to work a full day. The cell count was reduced from 145 to 6 per c.mm. The Wassermann reaction was changed from positive with 0.05 c.c. to positive with 0.4 c.c. Eighteen months have passed since the last treatment and the patient still feels well, his sight

and hearing are normal, his memory is good and he has no ataxia. He has worked every day during this period. The examination of his spinal fluid at the present time shows 6 cells per c.mm. and a positive Wassermann reaction with 0.4 c.c.

CASE 13.—A man, aged 44, entered the hospital Aug. 1, 1914. A diagnosis of general paresis of the insane was made. Six years before he had had a chancre, which was followed by a rash and severe headaches. He had been treated with potassium iodid and injections of mercury for about six months. Eight months before he had begun to have headaches, which had increased in severity and frequency. He had become nervous, irritable and unable to sleep. He had become deaf and had suffered from tinnitus. One week before he had become crazed and was unconscious for fifteen hours. Following that attack his headaches had been worse, dizziness had been troublesome and his memory had almost entirely failed.

Physical examination showed a tremor of the face, tongue and hands, characteristic handwriting, unequal and hyperactive reflexes.

The Wassermann reaction in both blood serum and spinal fluid was positive, with a spinal fluid cell count of 43 per c.mm.

He was given fifteen doses of salvarsan and fifteen intraspinal treatments with salvarsanized serum. The first five treatments were at weekly intervals, but later the interval was lengthened to one month. After the first five treatments all headache, dizziness, nervousness and irritability disappeared and he was able to sleep. The spinal fluid cell count was reduced to 5 per c.mm. After seven treatments he returned to work and said that he felt perfectly well. After the whole amount of treatment the Wassermann reaction in the spinal fluid changed from positive with 0.05 c.c. to positive with 0.4 c.c., with a spinal fluid cell count of 2 per c.mm. The blood serum still gave a positive Wassermann reaction. The patient went for three months without treatment, at the end of this time he had another attack of loss of consciousness. As the spinal fluid showed no relapse he was given six doses of salvarsan.

CASE 14.—A man, aged 45, entered the hospital Aug. 5, 1914. A diagnosis of tabes dorsalis was made. Three years before he had begun to have anorexia, gaseous eructations and regurgitation of food about three hours after meals. One year before he had begun to have severe burning pain in the epigastrium one or two hours after meals. He had also had occasional attacks of vomiting, which relieved the pain. His appetite had failed until only liquids were taken. He had been unable to work and had lost thirty pounds in the previous three months.

Physical examination showed unequal and irregular pupils, which reacted very little to light, and exaggerated knee jerks. The guaiac test in his stools was positive. Gastric lavage showed much stasis. There were two liters of fasting contents. The free hydrochloric acid was 34 and total acidity was 60. There was no blood or lactic acid, but there was much starch and yeast and many sarcinae.

Roentgen ray five hours after a meal with bismuth showed two thirds of the meal remaining in the stomach. Fluoroscopic examination showed gastric atony and occasional antiperistaltic waves. After ten hours about one half of the meal remained in the stomach and after twenty-four hours there was still a large residue. The Romberg test was positive. The gait was markedly ataxic. The Wassermann reaction in the blood serum was positive. The spinal fluid gave a positive Wassermann reaction with 0.1 c.c. and showed a cell count of 33 per c.mm. The diagnosis of gastric ulcer was at this time added to the diagnosis of tabes dorsalis.

He was given six doses of 0.5 gm. of salvarsan and five intraspinal treatments with salvarsanized serum at intervals of two weeks. After this at irregular intervals he was given four doses of salvarsan and six doses of salvarsanized serum intraspinally. After two treatments pain and vomiting dis-

appeared and his appetite improved. After five treatments very little stasis could be demonstrated either by tube or by Roentgen ray and he became free from symptoms. His condition of ataxia improved and he returned to work. After an interval of four months without treatment, although he was still free from symptoms, gastric lavage showed much stasis, free hydrochloric acid of 18 and total acidity of 60. After this, four treatments were given at intervals of three weeks. The cell count in the spinal fluid was reduced to 2 per c.mm. and the Wassermann reaction was changed so that 0.4 c.c. was necessary to give a positive test. The patient meanwhile began to lose strength and weight and was operated on two months later and a large retroperitoneal carcinoma involving the fundus of the stomach was found. Therefore the carcinoma was demonstrated four years after the first symptoms and two years after the first severe pain. It is of interest that his symptoms and stasis disappeared under antisyphilitic treatment and this led to the diagnosis of a syphilitic ulcer of the pylorus complicating the tabes. Ten months have elapsed since the last treatment and seven months since gastro-enterostomy was performed and the patient has gained much in strength and weight and works every day.

CASE 15.—A man, aged 62, entered the hospital May 31, 1914. A diagnosis of tabes dorsalis was made. He had had a chancre forty years before. For eighteen years he had had lancinating pains in his legs and for fourteen years increasing difficulty in walking. Recently he had had incontinence of urine and feces and had been able to walk only with two people to assist him.

Physical examination revealed signs diagnostic of advanced tabes dorsalis. The Wassermann reaction was positive in both blood and spinal fluid, with a spinal fluid cell count of 108 per c.mm.

He was given four doses of salvarsan and three treatments with salvarsanized serum intraspinally at weekly intervals. The last treatment was given nineteen months ago. During this time he has had less incontinence of urine and none of feces. He has had no pain and he can walk very well with one cane.

CASE 16.—A man, aged 35, entered the hospital March 23, 1914. A diagnosis of tabes dorsalis was made. Twelve years before he had had a chancre. Eleven days before he had had tingling and numbness in his fingers and toes and pains in his legs. For six days he had had trouble in walking. His gait had been unsteady and he had fallen repeatedly when he had turned or stopped suddenly. He had also had some dizziness, and had had a sense of pressure about his waist for several days.

Physical examination showed unequal and irregular pupils, which reacted to light. The deep reflexes of the arms and legs were absent. There was marked incoordination in all his movements. The Romberg test was positive.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 16.

He was given three doses of salvarsan and three treatments with salvarsanized serum intraspinally. This relieved the pain, numbness and dizziness completely. His ataxia was greatly decreased, and he was able to walk and to turn quickly without any trouble. His Romberg test was negative and coordination was much improved. The cell count in his spinal fluid fell from 16 to 3 per c.mm. Twenty-four months have elapsed since he was last treated and during this interval he has remained completely free from symptoms.

CASE 17.—A man, aged 52, entered the hospital Dec. 9, 1914. A diagnosis of tabes dorsalis was made. Twenty-five years before entrance he had had a chancre. For ten years he had had a tendency to stagger. For eight years he had had lightning pains in his legs and difficulty in starting his urine. For five years he had had difficulty in controlling his feet and had fallen several times. He had recently had some difficulty in controlling his rectal sphincter. He had had complete loss of sexual power for eight months. All his symptoms had been progressive.

Physical examination showed irregular, unequal pupils, which did not react to light, and absent knee jerks, a positive Romberg test and marked incoordination of the movements of both arms and legs.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 90 per c.mm.

He was given seven doses of salvarsan and six intraspinal treatments with salvarsanized serum. His pains were quickly relieved by treatment and gradually his legs and feet became stronger and more easily controlled. He could walk without falling or stumbling and felt greatly improved in every way. The spinal fluid cell count was reduced from 90 to 5 per c.mm. The Wassermann reaction in the spinal fluid was changed from positive with 0.2 c.c. to positive with 0.4 c.c. Twelve months have elapsed since the last treatment and there has been no return of symptoms.

CASE 18.—A man, aged 48, entered the hospital Nov. 17, 1915. A diagnosis of neurosyphilis was made. He had had a chancre several years before. For several months he had felt tired and irritable.

Physical examination was entirely negative, except for a blood pressure of 200 mm. of mercury.

The Wassermann reaction in both blood and spinal fluid was positive, with a spinal fluid cell count of 80 per c.mm.

He was given nine doses of salvarsan and six intraspinal treatments with salvarsanized serum. His tired feeling was relieved and his disposition became more nearly normal. The cell count in his spinal fluid was unaffected by three doses of salvarsan alone, but dropped to normal after three intraspinal treatments in conjunction with the salvarsan. After the last treatment the Wassermann reaction in his spinal fluid was positive with 0.4 c.c., while at entrance it was positive with 0.2 c.c.

Three weeks after the last treatment he developed lobar pneumonia and died.

CASE 19.—A woman, aged 46, entered the hospital Dec. 30, 1914. A diagnosis of tabes dorsalis was made. For five years she had had frequent attacks of severe headache and vomiting, which lasted for two or three days. For three years she had had shooting pains in the legs and for four months had had marked unsteadiness in gait. For three months she had been unable to pass her urine and had had to be catheterized. She recently had been very dizzy, nervous and depressed mentally.

Physical examination showed Argyll Robertson pupils, absent deep reflexes in both legs and a positive Romberg test.

The Wassermann reaction in both blood serum and spinal fluid was positive with a spinal fluid cell count of 12 per c.mm.

She was given six doses of salvarsan and five intraspinal treatments with salvarsanized serum. After the first treatment with salvarsan the spinal fluid cell count was 18 per c.mm., but directly after the first double treatment the cell count fell to 9 per c.mm. After further treatment all pains and dizziness disappeared and the cell count in the spinal fluid became normal. The mental depression disappeared, there was no sphincter disturbance and she felt well in every way.

One month after the last treatment she died of lobar pneumonia.

CASE 20.—A man, aged 33, entered the hospital Jan. 23, 1915. A diagnosis of tabes dorsalis was made. Ten years before he had had a chancre. For four years he had had pains radiating around the waist, indigestion, nausea and vomiting. During the four days previous to entrance he had had uncontrollable vomiting.

Physical examination showed absent deep reflexes in the legs and Argyll Robertson pupils.

The Wassermann reaction was positive in the blood serum. The spinal fluid showed a cell count of 16 per c.mm. and gave a positive Wassermann reaction with 0.2 c.c.

He was given seven doses of salvarsan and five intraspinal treatments with salvarsanized serum. After three doses of salvarsan the vomiting stopped. Further treatment relieved his pain and the spinal fluid cell count became normal. The Wassermann reaction was positive with 0.4 c.c.

One month after the last treatment he died of pneumonia.

CASE 21.—A man, aged 48, entered the hospital Oct. 27, 1914. A diagnosis of general paresis of the insane was made. He had had some local sores on his penis twenty-nine years before and again twenty years later. Five months before he had had a severe mental shock, following which he had acted queerly. He had imagined that he was suspected of killing his brother and had become so unbalanced mentally that he had been under restraint temporarily in an institution. For one week he had had numbness and tingling in his left ankle. He had also had severe headaches, failing memory and loss of energy.

Physical examination showed unequal pupils, which did not react to light. There was marked tremor of the face, lips and tongue, with exaggerated reflexes and a positive Romberg sign. The blood pressure was 240 mm. of mercury and the urine showed an abundance of albumin and a variety of casts.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 166 per c.mm.

He was given three doses of salvarsan and three intraspinal treatments with salvarsanized serum. The first treatment reduced the cell count from 166 to 11 per c.mm. After the final treatment the numbness and headache were relieved and he felt so well that he refused to return to the hospital. Four months later, following a cerebral hemorrhage, he became completely paralyzed and died.

CASE 29.—A woman, aged 55, entered the hospital Feb. 9, 1915. A diagnosis of tabes dorsalis was made. For four months she had noticed a staggering gait. For six weeks she had been dizzy and nauseated and had vomited frequently. Directly following one of the attacks of vomiting she had noticed numbness of the right side of her face and general weakness. Staggering recently had become much worse, her legs had felt numb and she had been upset mentally.

Physical examination showed unequal and irregular pupils, absent deep reflexes in the arms and hyperactive knee jerks.

The Wassermann reaction was positive in both blood and spinal fluid, with a spinal fluid cell count of 87 per c.mm.

She was given thirteen doses of salvarsan and twelve intraspinal treatments with salvarsanized serum. After the first five treatments there was complete relief of the numbness, weakness, staggering and mental confusion. The cell count in the spinal fluid was reduced to normal. After the tenth treatment she felt perfectly well. The Wassermann reaction in the spinal fluid changed from positive with 0.1 c.c. to positive with 0.4 c.c. Four months elapsed without treatment and there was no return of symptoms. Two more treatments were given recently in order to get specimens of the spinal fluid. This showed no further change.

CASE 36.—A man, aged 54, entered the hospital March 11, 1915. A diagnosis of general paresis of the insane was made. He had had a chancre twenty-eight years before and had had treatment for about seven years. He had had vague headaches for fifteen years and for ten years he had had dizziness, ataxia and joint pains. For ten months he had had progressive mental disturbance. He had been unable to sleep because of severe abdominal pain.

Physical examination showed Argyll Robertson pupils, sluggish and unequal deep reflexes in the legs.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 80 per c.mm. The pain, dizziness and vomiting

were relieved by treatment, but as the patient developed delusions all treatment was omitted. Two months after treatment was discontinued he became clear mentally and has continued so for seven months.

CASE 39.—A woman, aged 40, entered the hospital June 2, 1915. A diagnosis of *tabes dorsalis* was made. For fourteen years she had had shooting pains in the legs and for a year had been markedly ataxic. For the previous eight months she had been unable to walk about the house without a cane and during the last four months she had been bedridden. For six months she had had pains of such severity in her arms and legs that she had taken from 2 to 10 gm. of aspirin daily.

Physical examination showed unequal and irregular pupils, which did not react to light, and absent knee and ankle jerks. She was unable to stand alone.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 128 per c.mm.

She was given six doses of salvarsan and six intraspinal treatments with salvarsanized serum. All pain was relieved by the first two treatments. After the last treatment she was able to walk about the house without assistance. The changes in the spinal fluid were marked. The cell count became normal and the Wassermann reaction was changed from positive with 0.5 c.c. to negative with 1 c.c. After four months without treatment, during which time there was no return of symptoms, the patient was given four doses of salvarsan, because of a positive Wassermann reaction in the blood serum. The blood serum since that time has given a negative Wassermann test.

CASE 40.—A woman, aged 46, entered the hospital May 24, 1915. A diagnosis of *tabes dorsalis* was made. For six months she had had weakness of the legs, paresthesia and unsteadiness of gait.

Physical examination showed unequal and irregular pupils, absent deep reflexes in the legs and a positive Romberg test. The patient could barely stand alone.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 18 per c.mm.

She was given nine doses of salvarsan and nine intraspinal treatments with salvarsanized serum. The first five treatments reduced the cell count to normal and the Wassermann reaction was changed from positive with 0.2 c.c. to positive with 0.6 c.c. At this time she became able to walk about the house without difficulty. The last four treatments were given at irregular intervals of one and two months. At the last examination the Wassermann reaction in the spinal fluid was negative with 1 c.c. One month has elapsed since the last treatment. At present she is free from symptoms and is steadily improving in her ability to walk.

CASE 41.—A man, aged 40, entered the hospital June 25, 1915. A diagnosis of *tabes dorsalis* was made. For sixteen months he had been nervous and easily tired. For six months he had had numbness in the legs, loss of sensation in the feet and unsteadiness. He had had some difficulty in speech and severe frontal headaches.

Physical examination showed absent deep reflexes in arms and legs, ataxia in the right arm and leg and a positive Romberg test.

The Wassermann reaction was positive in both blood serum and spinal fluid, with a spinal fluid cell count of 60 per c.mm.

He was given seven doses of salvarsan and seven intraspinal treatments with salvarsanized serum. After three treatments the spinal fluid cell count was reduced to normal, headache disappeared, tremor lessened and nervousness was relieved. The last four treatments were given at monthly intervals. The ataxia has been much relieved by them and the Wassermann reaction has changed from positive with 0.3 c.c. to positive with 0.6 c.c. Two months have elapsed since the last treatment and there has been no return of symptoms.

CASE 43.—A man, aged 51, was admitted to the hospital June 18, 1915. A diagnosis of tabes dorsalis was made. Twenty-eight years before he had had a chancre which was followed by a generalized rash. He had been treated with mercury by mouth until he was salivated. For two years he had had some dizziness and trouble in walking. He had also had marked constipation and attacks of vomiting.

Physical examination showed unequal pupils, which reacted sluggishly to light, unsteady gait, ataxia of arms and a positive Romberg test.

The Wassermann reaction was positive in both blood serum and spinal fluid with a spinal fluid cell count of 41 per c.mm. He was given three doses of salvarsan, and three intraspinal treatments with salvarsanized serum. This relieved his dizziness and staggering and also his constipation and vomiting. During the next three months he gained twenty pounds. During the last three months he has had three doses of salvarsan and three treatments with salvarsanized serum. He is free from all symptoms. The cell count in the spinal fluid is normal. The Wassermann reaction is positive in both blood serum and spinal fluid.

CASE 44.—A man, aged 48, entered the hospital July 14, 1915. A diagnosis of tabes dorsalis was made. Seventeen years before he had had a chancre. Six months before he had begun to have severe headaches, weakness of the legs, retention of urine and progressive difficulty in walking. For one month before he had been unable to get out of bed. He had vomited frequently, had been nervous, irritable and very forgetful.

Physical examination showed absent deep reflexes in both arms and legs, ataxic gait, positive Romberg test and pupils which reacted very poorly to light.

The Wassermann reaction was positive in both blood and spinal fluid with a spinal fluid cell count of 33 per c.mm.

He was given five doses of salvarsan and four intraspinal treatments with salvarsanized serum. His headache, vomiting and irritability were relieved, and from being unable to get out of bed he improved so that he was able to work. His memory was greatly improved. He has had no treatment for six months. During this time he has been free from symptoms and has worked steadily.

CASE 45.—A man, aged 32, entered the hospital May 4, 1915. A diagnosis of cerebrospinal syphilis was made. Four weeks previous to admission he had had several temporary paralyses of his legs and arms and a more permanent paralysis of his face. For the past week he had had a feeling of constriction in his knees and inability to control his feet and legs and frequent crampy pains in his legs.

Physical examination showed that the left pupil was larger than the right. The knee jerks, Achilles, and epigastric reflexes were exaggerated. There was a double ankle clonus present. The Romberg was markedly positive. There was a spastic gait.

The Wassermann reaction in the blood was positive after a provocative reaction; in the spinal fluid it was negative except after salvarsan provocative, when it was positive with 1 c.c. The spinal fluid cell count was 15 per c.mm.

He was given two doses of salvarsan of 0.3 and 0.5 gm., respectively, three doses of 0.5 gm. each of salvarsan and three intraspinal serum treatments of 20 c.c. each; also three doses of salvarsan of 0.5 gm. each.

The 0.3 gm. of salvarsan produced a provocative positive blood Wassermann reaction and the 0.5 gm. produced a provocative positive Wassermann reaction in the spinal fluid in 1 c.c. amounts; however, the cell count and symptoms were not changed. The first double treatment reduced the cell count to 5 and the patient improved. The next two double treatments relieved all the symptoms and the spinal fluid became negative. Following this, three doses of 0.5 gm. each of salvarsan were given. Six months have elapsed and the patient is still free from symptoms.

CASE 46.—A man, aged 49, entered the hospital April 22, 1915. A diagnosis of tabes dorsalis was made. Eighteen years before he had had two primary sores. These were cauterized and he was given mercury by mouth and potassium iodid for three months. For the past two years he had had pins and needles sensation in his legs and arms. For the past year he had had squint and diplopia.

Physical examination showed that the pupils were inactive to light. The left pupil was larger than the right. There was optic atrophy in both pupils. The biceps and ankle reflexes were just obtainable. The knee jerks were active; the left being larger than the right. The plantar reflexes were exaggerated.

The Wasserman reaction was positive in the blood and spinal fluid, with a spinal fluid cell count of 44 per c.mm.

He was given seven doses of 0.4 gm. each of salvarsan and four intraspinal treatments of 25 c.c. each of salvarsanized serum in four months. The Wassermann reaction in the blood became negative; in the spinal fluid it was changed from positive with 0.4 c.c. to positive with 0.9 c.c., and the spinal fluid cell count was reduced from 44 to 3 per c.mm. The patient was relieved from symptoms and felt better than he had for years. He has been six months without treatment and without return of symptoms.

CASE 47.—A woman, aged 42, entered the hospital Aug. 31, 1915. A diagnosis of tabes dorsalis was made. She had had a chancre and rash twenty-one years before. Fourteen years before she had had a nervous breakdown, with shooting pains in her head, black spots before her eye and shaking all over. Since then she has had frequent knifelike pains across her abdomen, indigestion, and contractions of her lips, fingers, face and elbows. She had one spasm of her whole body. For the past sixteen years she has had shooting pains all over her body and varied indefinite symptoms. For the past year in addition she has had twitching of her eyelids, numbness of her fingers, and she has been sensitive to cold weather.

Physical examination showed that her pupils were inactive to light. The biceps, triceps, periosteoradial, right knee jerk and both ankle reflexes were absent. There was incoordination of the right hand and fingers.

The Wassermann reaction in the blood and spinal fluid was positive, with a spinal fluid cell count of 80 per c.mm.

She was given seven doses of salvarsan and four intraspinal treatments with salvarsanized serum. The first two doses of salvarsan reduced the spinal fluid cell count from 80 to 21, but did not change the Wassermann or improve the symptoms. After that, double treatments were given. The first two of these reduced the cell count to 3, and relieved the pain, numbness and indigestion. Following the remaining treatments the patient felt like a new person. The spinal fluid Wassermann reaction changed from positive with 0.1 c.c. to positive with 0.3 c.c. It is now two months since the last treatment.

CASE 48.—A man, aged 43, entered the hospital Sept. 27, 1915. A diagnosis of tabes dorsalis was made. Twelve years before he had had a chancre and loss of hair. For three and one-half years after that he was given iodid of mercury by mouth. One year before he had begun to have sharp shooting pains in his legs, pins-and-needles sensation in his arms and weakness of his knees. Later he began to stagger. Recently he has had urgency of micturition.

Physical examination showed the periosteoradial and epigastric reflexes absent, knee jerks and Achilles reflexes hyperactive, and the Romberg slightly positive.

The Wassermann reaction was positive in both the blood and spinal fluid, with a spinal fluid cell count of 37 per c.mm.

He was given six doses of 0.6 gm. each of salvarsan and five intraspinal treatments with salvarsanized serum in two months. The first two treatments relieved the pains. The other treatments relieved the paresthesia, weakness and urgency of micturition. The ataxia was greatly lessened, being practically

relieved. The spinal fluid cell count was reduced to 1, the Wassermann reaction from positive with 0.2 c.c. to positive with 0.5 c.c. It is now three months since treatment.

CASE 51.—A woman, aged 35, entered the hospital Aug. 6, 1915. A diagnosis of *tabes dorsalis* was made. Some years before she had had a chancre. Eight years before she had begun to have sharp, shooting pains in her legs. These increased in intensity until she acquired a morphin habit and took 4 grains of morphin daily. For the previous six years she had had nausea and vomiting accompanying frequent attacks of gastric distress. For the previous five years she had had an unsteady gait, unsteadiness when standing and increasing incontinence of urine until at the time of entrance she dribbled constantly. Eight months before her entrance her right knee cap had slipped out of place and the knee had become swollen and she developed a Charcot knee. For the previous four months she had walked a little with a crutch.

Physical examination showed her pupils reacted sluggishly to light. There was ataxia of the left hand. The biceps, triceps, knee jerks, Achilles and plantar reflexes were absent. She was unable to stand alone.

The Wassermann reaction was positive in both the blood and spinal fluid, with a spinal fluid cell count of 39 per c.mm.

She was given two doses of salvarsan and four intraspinal treatments with salvarsanized serum. The first two treatments relieved the pain and gastric distress somewhat. The morphin was reduced to 1 grain per diem. After the last treatment, which was three months ago, she was free from pain and the spinal fluid Wassermann reaction was positive with 0.6 c.c.

CASE 61.—A woman, aged 39, entered the hospital July 20, 1915. A diagnosis of *tabes dorsalis* was made. For the previous three years she had had pain in the large joints, and attacks of dizziness, nausea, and vomiting of ten days' duration. The attacks appeared every few months. For the past five months she had pain constantly and loss of appetite, strength and weight.

Physical examination showed that the pupils were irregular. All of her arm and leg reflexes were hyperactive.

The Wassermann reaction was positive in both the blood and spinal fluid, with a spinal fluid cell count of 27.

She was given eight doses of salvarsan and three intraspinal treatments with salvarsanized serum. The pains were relieved early, and there have been no attacks of dizziness. Salvarsan alone seemed to be of much benefit in this case.

CASE 64.—A man, aged 48, entered the hospital Oct. 11, 1915. A diagnosis of *tabes dorsalis* was made. Eleven years before he had begun to have incontinence of urine while asleep. This progressed until for the previous three years he had had to wear a urinal constantly. For the previous two years he had been ataxic and had been unable to see well at night. He had had alternating attacks of diarrhea and constipation. For the previous ten months he had had pain in the large joints and epigastrium, with edema of the ankles at night and dyspnea. Just previous to his entrance his hands and fingers had been numb with loss of sensation and ataxia of the fingers.

Physical examination showed the pupils to be pinpoint and inactive to light. The reflexes of the arms and legs were absent. There was marked ataxia and incoordination of the arms and legs. The gait was ataxic and stamping.

The Wassermann reaction was slightly positive in the blood; in the spinal fluid it was positive with 0.4 c.c. The spinal fluid cell count was 27 per c.mm.

He was given four doses of salvarsan and three intraspinal treatments with salvarsanized serum. Following this the serum became negative and on account of the edema of the ankles and albumin and casts in the urine only intraspinal serum treatments were continued. No change in the symptoms or in the spinal fluid Wassermann reaction followed the double treatments, although the cell count increased from 37 to 64 and fell back to 30, and the serum Wassermann reaction became negative. The first four intraspinal serum treatments alone

reduced the cell count to 3, changed the Wassermann reaction from positive with 0.4 c.c. to positive with 0.8 c.c. and somewhat relieved the incontinence. The pains were nearly relieved.

CASE 65.—A man, aged 46, entered the hospital Nov. 3, 1915. A diagnosis of cerebrospinal syphilis was made. Twelve years before he had had a chancre followed by a rash, sore throat and headache. At this time he was treated by mouth. Six years before a sudden weakness of the right side had developed. This was followed by recovery of the right arm and partial recovery of the right leg. For the previous six years he had had short attacks of dizziness, faintness and diplopia. These attacks were of ten hours' duration. For the previous year he had had some incontinence of feces. For the previous four days he had had much dizziness and diplopia, his speech had been slow and he had been very absent minded.

Physical examination showed the right pupil to be larger than the left. Diplopia was present. There was tremor of the hand, leg and arm. The reflexes on the right side were hyperactive. There was weakness of the right leg, a double ankle clonus and a positive Babinski and Oppenheim on both sides.

The Wassermann reaction was positive in both the blood and spinal fluid, with a spinal fluid cell count of 65 per cmm.

He was given seven doses of 0.6 gm. each of salvarsan and six intraspinal treatments with salvarsanized serum. The early treatments relieved the diplopia and dizziness and the patient became much clearer mentally. He then developed a sudden weakness of both legs and the incontinence which first cleared up again returned, but mentally he remained improved. The Wassermann reaction in the spinal fluid was modified from positive with 0.1 c.c. to negative with 2 c.c. The spinal fluid cell count became normal, but the blood Wassermann reaction remained positive.

TREATMENT WITH SALVARSAN

CASE 2.—A man, aged 59, entered the hospital July 20, 1913. A diagnosis of *tabes dorsalis* was made. The patient had had a chancre thirty-two years before and for the previous fourteen years had had severe pains in the legs and cramp-like contractions. For nine years he had had stiffness in the knees, inability to run, failing eyesight and inability to walk in the dark. The previous few years he had taken morphin regularly for the pains. Occasionally he had had incontinence of urine and feces.

Physical examination showed the pupils to be mere pinpoints and inactive to light. All reflexes were absent. There was marked swaying in the Romberg position and the gait was ataxic.

The Wassermann reaction in the blood serum and in the spinal fluid was positive. The spinal fluid cell count was 5 per c.mm.

Treatment consisted of five doses of 0.6 gm. of salvarsan at another hospital and six doses of 0.9 gm. of neosalvarsan here at weekly intervals. As no improvement resulted he was later given the Swift-Ellis treatment at another hospital with considerable improvement.

CASE 3.—A man, aged 46, entered the hospital May 8, 1913. A diagnosis of *tabes dorsalis* was made. The patient had had a chancre twenty-five years before, and had been treated with mercury by mouth for three years. For seventeen years he had had pain in the region of the urinary bladder and inability to pass his urine. For twelve years he had led a catheter life. For fifteen years he had suffered from shooting pains in his arms and legs and for the previous three years he had used about 16 gm. codein and 2.5 gm. morphin daily. Occasionally he had been troubled by diplopia.

Physical examination showed Argyll Robertson pupils. The deep reflexes of the arms and legs were absent and there was noticeable ataxia.

The Wassermann reaction in the blood serum was positive, in the spinal fluid negative. The spinal fluid cell count was 2 per c.mm.

Treatment consisted of six doses of neosalvarsan and six doses of salvarsan given during a period of seven months. There was considerably less pain at the end of this time and it was not necessary to use a catheter so frequently.

CASE 7.—A man, aged 52, entered the hospital Nov. 3, 1913. A diagnosis of cerebrospinal syphilis was made. During the month before entrance he had had severe headaches, dizziness and ringing in the ears. He had also suffered from nausea and vomiting. Several times he had fallen on the street.

Physical examination showed that all his reflexes were hyperactive.

The Wassermann reaction in the blood serum was positive. In the spinal fluid the Wassermann reaction was positive with 0.2 c.c. The cell count in the spinal fluid was 6 per c.mm.

He was given two doses of salvarsan of 0.3 gm. each and three doses of neosalvarsan of 0.9 gm. each. The treatments were given at weekly intervals. The headaches, dizziness and ringing in the ears were considerably relieved after the first two treatments. After the last treatment there was complete relief from all symptoms and there has been no return of any trouble up to the present time.

CASE 30.—A man, aged 32, entered the hospital Jan. 15, 1915. A diagnosis of tabes dorsalis was made. For eight years he had had constipation and pain in the region of his sacrum. For several months he had been unable to empty his bladder and had been repeatedly catheterized.

Physical examination showed a sluggish reaction of his pupils to light, absent knee jerks and a positive Romberg test.

The Wassermann reaction in the blood serum was negative. In the spinal fluid a cell count of 22 per c.mm. was found. The Wassermann reaction in the fluid was positive with 0.2 c.c.

He was given four doses of salvarsan of 0.5 gm. each. There was no improvement in his symptoms and there was no change in the findings in the spinal fluid.

CASE 37.—A man, aged 30, entered the hospital June 28, 1915. A diagnosis of syphilitic meningitis was made. He had had a chancre eight months before coming to the hospital, which was followed by a generalized rash, sore throat and alopecia. He had taken mercury by mouth and potassium iodid for five months. For ten days he had had severe pains across the abdomen and extremely severe headaches, which had prevented sleep.

Physical examination showed a stiff neck and positive Kernig's sign. The Achilles tendon was absent on the right. His temperature was 104 F. and his pulse rate averaged about 120 per minute.

The Wassermann reaction was positive in both blood and spinal fluid. The cell count in the spinal fluid was 940 per c.mm. A differential count showed 62 per cent. of these cells were small mononuclears, 35 per cent. large mononuclears and 3 per cent. polymorphonuclears.

He was given five doses of salvarsan. After the first three doses all symptoms disappeared. The spinal fluid cell count was reduced from 940 to 33. The Wassermann reaction in the spinal fluid was changed from positive with 0.5 c.c. to positive with 1 c.c. The last treatment was five months ago. The patient has not been heard from since that time.

CASE 52.—A man, aged 21, entered the hospital Sept. 10, 1915. A diagnosis of cerebrospinal syphilis was made. For four years he had had headaches and occasional attacks of dizziness. The headaches had increased in severity during the previous year and later he had had attacks of vomiting. Ten days before weakness and stiffness of the right arm had appeared and his vision had become blurred. Six days before he had suddenly become unable to talk and he had noticed also that the right side of his face had become paralyzed. During the previous two days he had noticed some improvement, although he had had no treatment except rest in bed.

Physical examination showed marked weakness of the extensor muscles of the right arm. The reflexes of both arms and of the right leg were greatly exaggerated. The reflexes of the left leg were not increased. There were posi-

tive Babinski, Oppenheim and Gordon signs on both sides. There was a marked disturbance of his speech.

The Wassermann reaction was positive in both blood and spinal fluid. The cell count in the spinal fluid was 98 per c.mm.

He was given six doses of 0.5 gm. salvarsan at weekly intervals. After the first three doses all of his symptoms were relieved and the cell count in his spinal fluid was reduced to 60 per c.mm. The next three doses of salvarsan reduced the cell count to 9. The Wassermann reaction in the spinal fluid previously positive with 0.3 c.c. became negative with 2 c.c., but the blood serum remained positive. Four months have elapsed since treatment.

CASE 63.—A woman, aged 45, entered the hospital Nov. 24, 1915. A diagnosis of cerebrospinal syphilis was made. The patient had had a chancre five years before. Two years before she had had some loss of strength and periods during which she was incontinent of both urine and feces. One month previous to entrance she had had a sudden attack of weakness of the left leg. Two weeks later she had developed intense headaches which had prevented sleep and had confined her to bed. Her eyesight had failed rapidly.

Physical examination showed unequal pupils, which reacted sluggishly to light. All the deep reflexes of the arms and legs were hyperactive, particularly on the left side. There was some ataxia in the movements of the left arm and hand.

The Wassermann reaction in both blood and spinal fluid was positive, with a cell count in the latter of 42 per c.mm.

She was given nine doses of 0.4 gm. salvarsan at weekly intervals. The first two doses of salvarsan relieved her headache and improved the condition of her leg to some extent. After five doses of salvarsan she became able to walk on the street and only the closest inspection revealed any spasticity of the left leg. The Wassermann reaction in the spinal fluid was not modified, but the cell count was reduced from 42 to 4 per c.mm. After four more doses of salvarsan the Wassermann reaction in the spinal fluid was changed from positive with 0.1 c.c. to positive with 0.3 c.c. There was no effect on the Wassermann reaction in the blood serum.

CASE 71.—A man, aged 33, entered the hospital Dec. 10, 1915. A diagnosis of cerebrospinal syphilis was made. Four years before he had had a chancre. He had developed a generalized rash five months before with general weakness, headache and pain in his legs.

Physical examination showed a generalized maculopapular rash and general glandular enlargement. In addition he had some photophobia and all the deep reflexes of the arms and legs were exaggerated.

The Wassermann reaction in the blood serum and in the spinal fluid with 0.8 c.c. was positive. The cell count in the spinal fluid was 51 per c.mm.

Treatment consisted of six doses of 0.6 gm. of salvarsan at weekly intervals. At the end of this course of treatment the rash had disappeared and all of his symptoms had cleared up. The Wassermann reaction in the spinal fluid became negative with 1.5 c.c. of fluid, and the cell count dropped from 51 to 7 per c.mm. The Wassermann reaction in the blood serum was not altered.

CASE 72.—A man, aged 45, was admitted to the hospital Dec. 14, 1915. A diagnosis of cerebrospinal syphilis was made. Twenty years before he had had a chancre, which was followed by a generalized rash and some loss of hair. He had had no treatment other than two months of mercury by mouth. He had had no further manifestations of syphilis up to one year before, when his vision began to fail.

Physical examination showed an inequality of pupils with exaggerated deep reflexes in both legs.

The Wassermann reaction in both blood serum and spinal fluid was positive. The cell count in the spinal fluid was 30 per c.mm.

He was given five doses of 0.6 gm. salvarsan without any change in his symptoms or signs and without any effect on his cell count or Wassermann reactions. At the end of this time he was treated by the Swift-Ellis method.

TREATMENT WITH SALVARSANIZED SERUM INTRASPINALY ALONE

CASE 4.—A man, aged 38, entered the hospital Oct. 9, 1913. A diagnosis of *tabes dorsalis* was made. Sixteen years before he had had a chancre and had been treated with mercury by mouth for nine months. Ten years before he had had a sore mouth and had been treated with mercury and with potassium iodid for nine months. Nine months before he had had an ulcer in his throat, had felt run down and tired out. Because of this he had been treated for several months with mercury by mouth and intramuscularly but without relief. During the four months before entrance he had been given twelve doses of neo-salvarsan of 0.9 gm. each. The first four doses had for a short time relieved his symptoms, he had then begun to have pain in the back of his head and neck, and in his legs and abdomen. All of this trouble had developed while he was being treated vigorously with mercury and salvarsan and consequently he had become very despondent.

Physical examination showed no signs of disturbance in his reflexes. The Wassermann reaction was negative in his blood serum and also in his spinal fluid with 0.5 c.c. The spinal fluid showed a cell count of 10 per c.mm., and gave a doubtful globulin test (Noguchi). He was discharged from the hospital, with a diagnosis of overtreatment and apprehension.

He was readmitted Jan. 19, 1914. At that time he stated that he had had no treatment since the previous admission, that all his symptoms had become steadily worse, that he had developed very severe headaches, that he had been restless and irritable and had repeatedly thought of committing suicide because of the agonizing pains in his legs, neck and head.

Physical examination showed small irregular pupils, which reacted very little to light, and some drooping of the left eyelid. He was evidently very much upset, very nervous and irritable.

The spinal fluid showed a cell count of 15 per c.mm. and gave a positive globulin test (Noguchi). The Wassermann reaction was positive with 0.4 c.c.

On January 22 he was given the first treatment with salvarsanized serum. The cells in the spinal fluid were reduced from 15 to 10 per c.mm. and the headaches were improved. On January 29 the second treatment was given. After this the pains began to diminish in frequency and intensity. On February 4 the third treatment was given. This entirely relieved him of headaches. The cell count in his spinal fluid was reduced to 4 per c.mm. The spinal fluid gave a positive Wassermann reaction with 0.5 c.c. On February 11 a fourth treatment was given. Following this he had a few indefinite pains. At this time a decided mental change could be noted. Instead of staying in bed all day he became anxious to get up and about and seemed much encouraged. On February 13 he was given 0.3 gm. of salvarsan intravenously. This was followed by a bad reaction. The cell count in his spinal fluid rose to 15 per c.mm. and he went back to bed. He refused to take more salvarsan after this experience. On February 18 he was given the fifth intraspinal treatment. On February 25 he was given the sixth treatment and following this he began to improve again. The cell count in his spinal fluid at this time was 10 per c.mm. He was given additional intraspinal treatment on March 5, 12, 19 and 26. After the treatment on March 26 the spinal fluid cell count was positive with 0.6 c.c. He was then discharged, although he still complained at times of slight pain in his arms. Additional intraspinal treatment was given on April 5, 12, 19 and 26. After that time he became free from all symptoms, gained weight and walked several miles daily. Further treatment was given on May 3, 9 and 16. After the treatment on May 16 he began to work regularly. The spinal fluid showed a normal cell count and gave a positive Wassermann reaction with 0.8 c.c. On May 24 he was given the eighteenth intraspinal treatment and on June 5, 13, 23 and 30, on July 7 and 26 and on August 16 he was given further treatment intraspinaly. The treatment on August 16 was his twenty-fifth. After that time he worked days and night as a police detective, walking from six to

fourteen miles daily. He ate and slept irregularly, but had no symptoms, and felt better than he had for several years. The spinal fluid showed a normal cell count and gave a positive Wassermann reaction with 1 c.c. Treatment was then omitted for two months. On October 10 he was given the twenty-sixth treatment, and on December 12 the twenty-seventh. At that time his spinal fluid gave a negative Wassermann reaction with 1 c.c. and showed a normal cell count. On Jan. 19, 1915, he was given additional treatment. Three months later, April 18, he was given the twenty-ninth treatment. The spinal fluid at that time showed a cell count of 2 per c.mm., the Wassermann reaction was negative with 2 c.c., and the globulin test and the colloidal gold test were negative. He had no symptoms of any kind.

A total of twenty-nine intraspinal treatments were given, the first twenty-three at weekly intervals. The first four treatments relieved the severe pains in his head, neck, abdomen and legs, headache and sleeplessness, only indefinite pains remaining. He was out of bed and walking about the ward. The spinal fluid showed a reduction in cells from 15 to 4. The Wassermann reaction was changed from positive with 0.4 c.c. to positive with 0.5 c.c. The next six treatments reduced the cells to 1 per c.mm. and the patient was able to go home with only occasional indefinite pains, and he began to take long walks. The next six treatments reduced the Wassermann reaction to positive with 0.8 c.c. The patient began to work and to put on weight. The next eight treatments reduced the Wassermann reaction to positive with 1 c.c. Treatments were given at two monthly intervals for the next two times. The Wassermann reaction became negative with 1 c.c. The globulin test and the colloidal gold test were negative and the patient was free from all symptoms. The pupils did not return to normal. Thus, the symptoms cleared up and the cell count returned to normal quickly, but the Wassermann reaction became negative more slowly. Although an early case, it is interesting to note the rapid changes in symptoms and in pupils during the three months interval between the first two admissions. A more interesting point is that the patient grew worse while under intensive treatment with neosalvarsan and intramuscular mercury, but four intraspinal treatments relieved the symptoms. Twelve months have elapsed since the last treatment. The patient has worked every day and is free from symptoms. The Wassermann reaction in the blood serum is negative and in the spinal fluid it is negative with 2 c.c.; the cell count is 2 per c.mm.

CASE 12.—A man, aged 45, entered the hospital Nov. 3, 1913. A diagnosis of cerebrospinal syphilis was made. He had had a chancre eight years before. For two years he had had mucus discharge from his nose and photophobia. For the previous year he had had failing vision, until at entrance he could make out only moving objects close to his eyes. He had had dizziness and nausea. He had taken quantities of mercury and potassium iodid and many doses of salvarsan without effect. He had been entirely incapacitated for work.

Physical examination showed hypertrichosis, optic atrophy, pupils which reacted to light, deafness in the left ear, enlargement of the hands, wrists and ankles.

The Wassermann reaction in the blood serum was negative, in the spinal fluid it was positive with 0.3 c.c. The spinal fluid cell count was 15 per c.mm.

At weekly intervals he was given thirteen intraspinal treatments and with the last three intraspinal injections he was given three doses of salvarsan. After the treatment outlined the Wassermann reaction changed from positive with 0.3 c.c. to positive with 0.7 c.c. and the cell count in the spinal fluid varied between 43 and 9. There was relief of headache and slight improvement in vision. The improvement lasted for eight months. The Roentgen-ray findings together with the symptoms and signs pointed to acromegaly and the above treatment was undertaken to rule out a possible syphilitic basis. There was insufficient evidence of pituitary tumor to warrant any operation except decompression. Two years have elapsed since the last treatment and he has worked every day.

CASE 22.—A man, aged 42, entered the hospital, and on examination a diagnosis of *tuberculous dorsalis* was made. He had had a chancre twenty-three years before, followed by a rash, sore throat and alopecia. He had been treated with mercury by mouth for three years. Twelve years before he had begun to have shooting pains in his legs. Seven years before he had noticed that he could not run and that he had difficulty in walking at night. He had taken twenty doses of salvarsan in the previous two years, each treatment helping for a short time only.

Physical examination showed unequal pupils, which did not react to light, absent deep reflexes in the legs, positive Romberg test and ataxia of the hands and feet.

The Wassermann reaction in the blood serum was negative; in the spinal fluid it was positive with 1 c.c. and there was a cell count of 7 per c.mm.

The patient was given nine doses of salvarsanized serum intraspinally. The first intraspinal treatment produced a provocative Wassermann reaction in the spinal fluid, a positive reaction with 1 c.c. becoming positive with 0.5 c.c. The eight following treatments changed the Wassermann reaction back to positive with 1 c.c. Pain, numbness, and ataxia were relieved, but following the last treatment there was a slight return of the ataxia which is clearing up.

CASE 23.—A man, aged 18, entered the hospital Nov. 29, 1914. A diagnosis of syphilitic meningitis was made. Six months before he had had two primary sores, followed by a rash. He had taken mercury and potassium iodid for three months and had had three intravenous doses of salvarsan just previous to entrance to the hospital. For one month he had had a sore throat, sore eyes, headache, pain in his chest and abdomen, vomiting, internal strabismus of the right eye, diplopia, and poor vision. For one week he had had nocturia and dizziness and for four days he had had weakness of the right leg, tremor of the left hand and severe headache. The three doses of salvarsan had not relieved any of his symptoms.

Physical examination showed a retinitis and internal strabismus of both eyes, ptosis of the right eye, left knee jerk exaggerated and greater than the right, neck stiff and painful, Oppenheim positive on the right side, double Kernig, Romberg slightly positive, ankle clonus on the left side and ataxia of the arms and legs.

The Wassermann reaction in the blood serum was negative; in the spinal fluid it was positive with 0.1 c.c. The spinal fluid cell count was 550 per c.mm.

On November 29, December 5 and December 9 he was given salvarsan 0.2 gm., 0.4 gm. and 0.6 gm. intravenously and during this time he was given six doses of intramuscular mercury and 30 drops of saturated solution of potassium iodid three times daily. During this two weeks of treatment the headache and diplopia became less, but there were no changes in the physical signs or in the spinal fluid cell count.

December 10 he was given the first intraspinal treatment. This entirely relieved his headache and diplopia. On December 15 the second treatment was given. The cells were reduced from 533 to 272 per c.mm and the stiffness of

the neck and positive Kernig's sign disappeared. He was let out of bed and discharged from the hospital. On December 22 the third treatment was given and the cells were reduced to 100 and there were no symptoms remaining. The Wassermann reaction was positive with 0.2 c.c. On December 29 the fourth treatment was given. The patient went to five dances the following week and danced every dance. On January 1 the fifth treatment was given. He then began to work. On January 12 and 19 the sixth and seventh treatments were given. They were followed by severe headache and pains. On January 26 the eighth treatment was given. On February 2 the cells were 42 and the Wassermann reaction was positive with 0.4 c.c. Although free from symptoms and with the Wassermann reaction diminishing, the cell count varied between 40 and 50 for four weeks, therefore treatments were given less frequently. On February 16 the cells were 14; on March 2 they were 10 and the Wassermann reaction was positive with 0.5 c.c. On March 13 the patient was given the twelfth treatment, and the cells were reduced to 5. During that week the patient had three convulsions. On March 25 he was given the thirteenth treatment, the cells being 7. On April 10 he was given the fourteenth treatment; the cells were 9 and the Wassermann reaction was positive with 0.6 c.c. On May 1 the fifteenth treatment was given. The spinal fluid cell count was 6 per c.mm. On June 5 the sixteenth, and on July 8 the seventeenth treatment was given. The spinal fluid at this time showed a cell count of 6 per c.mm. and gave a negative Wassermann reaction with 1 c.c., but the blood Wassermann reaction became positive. Therefore salvarsan was given for five doses, until the blood serum became negative, and the spinal fluid remained negative with a cell count of 3. Four months have elapsed since the treatment and there has been no return of symptoms. The patient has worked every day.

It is seen that salvarsan, mercury and potassium iodid did not prevent the symptoms of syphilitic meningitis previous to entrance to the hospital, neither did similar intensive treatment improve symptoms of the spinal fluid findings in the hospital; yet two intraspinal treatments relieved all the patient's symptoms, reduced the cell count to 100 and he was able to go home. The third treatment reduced the cells to 50 and he returned to work. Although he was free from symptoms and the Wassermann reaction was rapidly becoming negative, the cells remained between 40 and 50 during the next four treatments, therefore treatments were given less frequently. The next seven treatments rendered the Wassermann reaction negative in 1 c.c. amounts, the cell count normal and the patient was to be given no further treatment; but it was found that the blood repeatedly negative had become positive, so that six doses of salvarsan were given until the blood became negative. The evidence of active syphilis in the blood may explain the convulsions while he was under intraspinal treatment. The fact that the blood previously negative should become positive while under intraspinal treatments is interesting. A similar occurrence has been noted in one other case in this series.

CASE 24.—A man, aged 41, entered the hospital June 26, 1914. A diagnosis of *tabes dorsalis* was made. He had had a chancre twelve years previously. For the past four years he had had attacks of abdominal pain at first at from five to six months' intervals and these had gradually become more frequent until during the previous year the attacks had occurred every month and for

the previous few months the attacks had come every week. These attacks of pain usually lasted several days, were paroxysmal in type, sharp and knifelike and were accompanied by retching and vomiting. He had marked constipation, the bowels not moving oftener than once a week. Two doses of salvarsan had been given at another hospital without relief of the pain or vomiting and he had been operated on for intestinal obstruction. The patient entered this hospital during an attack of gastric crisis.

Physical examination showed that the pupils were irregular and inactive to light, that there was some deafness in the right ear and that all deep reflexes of the arms and legs were hyperactive. Bismuth Roentgen-ray studies of the intestinal tract showed marked contraction and deep peristaltic waves. The Wassermann reaction in the blood serum was negative, but in the spinal fluid it was positive with 0.4 c.c., with a spinal fluid cell count of 5.

On June 18 during an attack of gastric crisis the patient was given intravenous salvarsan without relief, but on June 25 during another attack of gastric crisis the patient was given salvarsanized serum intraspinally, and in a few hours the pain and vomiting were relieved, the bowels moved every day thereafter and bismuth Roentgen ray gave normal intestinal findings. After a second intraspinal treatment on June 30 he was free from gastric crisis for three weeks, during which time he was able to eat everything and he gained 11 pounds in weight. On July 28 the gastric crisis returned and again salvarsan was given without relief. On August 8 during an attack of gastric crisis a third intraspinal treatment relieved all symptoms and the bowels became regular. On August 21, following a fourth intraspinal treatment, all symptoms were relieved for four weeks. For the next five months the patient was practically free from pain, at the end of which time he was given a fifth treatment and the spinal fluid showed 3 cells and a positive Wassermann reaction with 0.7 c.c. Following this treatment he had a severe reaction lasting for one day and the spinal fluid cell count increased to 87. On February 2 a sixth treatment was given, on February 9 a seventh, and on February 16 the eighth and final treatment was given. After this treatment the patient was free from pain, the cells in the spinal fluid became normal and the Wassermann reaction in the spinal fluid became negative with 1 c.c.

In this case on three separate occasions intravenous salvarsan had no influence on the gastric crisis, but intraspinal treatment promptly relieved all symptoms for three and four weeks' duration and later treatments entirely relieved the severe pain. The Wassermann reaction in the spinal fluid was changed from positive with 0.4 c.c. before treatment to negative with 1 c.c. after eight treatments. One year has elapsed since treatment was stopped and the patient has been free from gastric crises.

CASE 25.—A man, aged 48, entered the hospital Aug. 14, 1914. A diagnosis of *tabes dorsalis* was made. For five years he had had lightning pains in the abdomen and in the legs; for the previous two years he had had a constriction around the waist, dizziness, ataxia in the dark and inability in starting his urine; for the previous eight months he had had numbness of the left hand, severe girdle pains, failing eyesight and incontinence of urine and feces. He entered the hospital because of unbearable girdle pains.

Physical examination showed that the right pupil was larger than the left and inactive to light, and that both disks were of a chalky white; that the knee jerks were absent, and the Romberg was positive. There was ataxia and incoordination of the left leg, and areas of anesthesia were present over both legs. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.2 c.c. The spinal fluid cell count was 20.

On August 14 the first intraspinal treatment was given and the girdle pains were relieved and the cells in the spinal fluid were reduced to 3. On August 19 a second treatment relieved the dizziness and numbness and the cell count remained 3. On August 28 a third treatment was given; at this time the patient was less ataxic and felt stronger and the cell count was 0. On September 5 a fourth treatment was given, all symptoms were relieved and the patient was able to walk well. Following a fifth treatment on September 22 further treatment was omitted for two months. At the end of this time, on November 19, he was given a sixth treatment and was still free from all symptoms; he had no incontinence of urine and feces and the cell count was 6. On January 5 the seventh treatment was given and the patient had begun to work. On February 16 the eighth treatment was given and the patient was able to walk without trouble in the light and could walk very well in the dark; the cell count was 3. Treatment was omitted for four months. On June 10, although he was still free from symptoms, a ninth treatment was given, the cell count was 4. On July 8 a tenth treatment was given; the patient was free from symptoms, the cell count was 3, but the spinal fluid was positive with 0.2 c.c.

The first intraspinal treatment reduced the spinal fluid cell count from 20 to 3 and relieved the severe girdle pains; the first four treatments relieved all symptoms except the incontinence of urine and feces and these were relieved following the sixth treatment. Ataxia and incoordination rapidly improved. In spite of the marked improvement and the relief of all symptoms and a constant normal cell count, still the Wassermann reaction in the spinal fluid was uninfluenced by ten intraspinal treatments. This is contrary to the findings in the other cases. Ten months have elapsed since treatment, with no return of symptoms.

CASE 26.—A man, aged 35, entered the hospital Oct. 8, 1914. A diagnosis of tabes dorsalis was made. Fifteen years previously he had had a chancre followed by a rash and sore throat and had been treated with potassium iodid and mercury by mouth for three months. For the previous ten years he had had shooting pains in the legs every four or five weeks; for the previous two years he had had ataxia and failing vision, both of which were worse at night; for the past few months he had had partial paralysis and numbness of the right side of the body and occasional attacks of vomiting. The difficulty in walking had gradually increased until at the time of entrance he was unable to walk alone and the severe pains in the chest and the abdomen were constant, the pains in the legs occurring nearly every day.

Physical examination showed that the left eye did not react to light, that there was ptosis of the right eyelid and that there was internal strabismus and partial optic atrophy of both eyes. The knee jerks, the abdominal and the cremasteric reflexes were absent and there was a suggestive Babinski sign. Romberg sign was positive, there was incoordination of the left hand and arm and the patient was unable to walk alone. The Wassermann reaction in the blood serum was questionable and in the spinal fluid it was positive with 0.2 c.c., with a spinal fluid cell count of 40.

On October 10 the first intraspinal treatment with salvarsanized serum was given. On October 17 the second treatment relieved all pain and reduced the cell count to 14. On October 26 the third treatment was given and the cells in the spinal fluid were reduced to 5 and the patient felt well. On November 3 the fourth treatment was given and the spinal fluid showed a positive Wassermann reaction with 0.3 c.c. and a cell count of 16; on account of the latter condition

treatment was omitted for one month. On December 8 and 15 the fifth and sixth treatments were given. The patient was still free from pain, was less depressed and the paralysis and numbness were relieved. The cell count was 4, but he was more ataxic. On December 22, 29 and January 5 he was given the seventh, eighth and ninth treatments. The spinal fluid cell count was 1 and the Wassermann reaction was positive with 0.4 c.c. Although the patient was free from pain and was able to see better, the cell count was only 1 and the Wassermann reaction was weaker, still he was more ataxic and consequently further treatment was postponed. During the next few months the ataxia gradually decreased until the patient could walk with the aid of a cane, could drive horses and an automobile and was able to attend to a country medical practice. His eyesight improved so much that he discarded his glasses. On August 5, seven months after the last treatment, he was given the tenth intraspinal treatment and the spinal fluid showed 2 cells and a negative Wassermann reaction with 1 c.c. On August 12 he was given the eleventh treatment. Because his blood Wassermann reaction had always been questionable he was given two doses of salvarsan of 0.3 gm. each and further treatment was discontinued.

The first three treatments relieved all pain, numbness and vomiting and the spinal fluid cell count was reduced from 40 to 5. Five treatments were required to change the Wassermann reaction from positive with 0.2 c.c. to a positive with 0.3 c.c., and five more treatments were required to change it from 0.3 c.c. positive to 0.4 c.c. positive. Although the patient was relieved of all symptoms except ataxia, the latter progressively increased. During the next few months, however, without treatment the ataxia gradually decreased until he was able to conduct his practice. Thirteen months have elapsed without return of symptoms; the patient is able to walk unassisted and the spinal fluid shows a cell count of 1 and the spinal fluid Wassermann reaction is negative with 1 c.c.

CASE 27.—A man, aged 35, entered the hospital Oct. 14, 1914. A diagnosis of *tabes dorsalis* was made. Eight months before he had noticed that his knees were stiff on going up stairs, and a little later that he staggered when walking on a level. At this time he also noted a constriction about the abdomen and paresthesia in the legs, and he was very irritable. Six months before entrance he had developed incontinence of urine, had had difficulty in writing, and in buttoning his clothes, had been unable to keep his balance with his eyes closed and had had some dizziness. For the previous four months he had had sharp, shooting pains in the legs and has become helpless in the dark. For the previous two months he had been unable to walk alone and only with great difficulty when taking some one's arm. He was unable to walk at all on an uneven surface.

Physical examination showed that all deep and superficial reflexes were absent and Romberg test was positive; in fact he could not stand alone. There was marked ataxia and incoordination of the arms and legs. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.4 c.c., and the spinal fluid cell count was 210.

On October 22 the first treatment of salvarsanized serum was given and the cell count was reduced to 100. On October 28 the second treatment relieved dizziness, lessened the pain and reduced the cells to 37. On November 4 the third treatment was given and improvement in walking was noted. On November 11 the fourth treatment caused a severe reaction with excessive pain, and the cell count increased to 165, so that treatment was omitted for three weeks. On December 2 the fifth treatment relieved the pain, reduced the cell count to 50

and the Wassermann reaction became positive with 0.5 c.c. On December 9, 15 and 22, respectively, the sixth, seventh and eighth treatments were given, during which time the cell count varied between 36 and 50. The last treatment caused a severe reaction, so treatment was omitted for two weeks. On January 5 the ninth treatment was given and it was noted that the patient could walk better and that the spinal fluid Wassermann reaction was positive with 0.7 c.c. On January 12 the tenth treatment caused a bad reaction and the cell count increased to 75. As this had happened three different times further treatment was given at two-week intervals. On January 26 the eleventh treatment was given and the patient was free from pain and could walk a little alone, the spinal fluid showing 33 cells and a positive reaction with 0.8 c.c. On February 9 the twelfth treatment was given and the patient was able to walk on the street alone. On February 24 the thirteenth treatment was given and on March 9 the fourteenth treatment; the spinal fluid showed 16 cells and a positive Wassermann reaction with 1 c.c., and the patient could walk with a cane at will. On April 1, 15, and May 12 treatments were given; the patient was able to walk without a cane, the spinal fluid showed 8 cells and a negative Wassermann reaction with 1 c.c. On June 2 and 23 the eighteenth and nineteenth treatments were given. Six weeks later, on August 5, the twentieth treatment was given and on August 12 the twenty-first and last treatment was given. At this time the spinal fluid showed 5 cells and a negative Wassermann reaction with 2 c.c. The patient began to work and has continued to do so since the last treatment, eight months ago without untoward symptoms.

This case was evidently one of rapid onset and of a very active process, since only one and one half years elapsed between the first minor symptom of stiffness and the final symptom of paralysis; the activity of the process is further evidenced by the high cell count of 210 for a case of tabes. The first three treatments relieved the pains and dizziness and were followed by slight improvement in the paralysis and by a reduction in the spinal fluid cells from 210 to 37. On account of the severe reactions following treatment the interval between these was increased from one to two weeks. When these severe reactions occurred the spinal fluid cells increased, although the Wassermann reaction steadily improved. Following the two week interval between treatments, no bad reactions resulted, the cell count slowly became normal, the Wassermann reaction rapidly became negative and the patient rapidly improved in locomotion until he was able to work. It required twenty treatments to render the patient able to walk a mile without aid and to reduce the spinal fluid cells to normal and to give a negative Wassermann reaction with 2 c.c. Eight months have elapsed since the last treatment, and he has had no return of symptoms and has worked every day since.

CASE 31.—A negro woman, aged 33, entered the hospital Oct. 22, 1914. A diagnosis of tabes dorsalis was made. Sixteen years previous she had had a generalized rash which disappeared under mercury treatment by mouth. For the previous three years she had noticed that she became very nervous and that her eyesight was failing. Two years before she had begun to have shooting pains in the head and eyes; one year before the shooting pains had appeared in her legs. Four years before her entrance she had begun to develop a staggering gait. At the time of admission she was unable to walk alone, was able

to see only the fingers held close to her eyes, was unable to sleep because of the very sharp pains in her legs.

Physical examination showed that the pupils did not react to light and that optic atrophy was present in both eyes. The deep arm reflexes were hyperactive and the deep leg reflexes were absent. Romberg test was positive and the patient was barely able to stand alone. In the blood serum the Wasserman reaction was negative and in the spinal fluid it was negative with 1 c.c., and the cell count was 27 per c.mm.

An intraspinal injection of salvarsanized serum on October 22 caused a severe reaction of pain, but reduced the cells in the spinal fluid from 27 to 13. On November 3 a second treatment relieved all pain, so that the patient could sleep well and the cells were further reduced to 7. On November 17, a third treatment was given, and the patient was able to see large objects which could not be seen previously; she could walk alone, in fact walked into the hospital unassisted. Fourteen months have elapsed since the last treatment.

CASE 32.—A woman, aged 38, entered the hospital Dec. 22, 1914. A diagnosis of tabes dorsalis was made. For the previous two years she had had sharp pains over the whole body and gradually the pains had increased in frequency until at entrance to the hospital they were constant in the legs and abdomen and were so severe as to prevent sleep, and large doses of aspirin gave little relief. The skin had become sore to the touch and the patient had become very nervous and irritable. She had had occipital headaches of a week's duration for some time.

Physical examination showed that both pupils were pinpoint and inactive to light. The deep and the superficial reflexes were absent in both arms and legs. In the blood serum the Wassermann reaction was negative and in the spinal fluid it was negative with 1 c.c.; the spinal fluid showed a cell count of 60 per c.mm.

On December 29 an intraspinal injection of salvarsanized serum nearly relieved the pain and did relieve the headache and reduced the spinal fluid cell count from 60 to 23. Following a second treatment, on January 5, all pain was relieved and the patient was able to eat and sleep well and she felt well. Following a third treatment, on January 19, the spinal fluid cell count became normal and the patient was still free from all symptoms. Thirteen months have now elapsed.

CASE 33.—A man, aged 38, entered the hospital Oct. 17, 1914. A diagnosis of tabes dorsalis was made. He had had a chancre eight years before. For the previous year he had had diplopia and general weakness, both of which symptoms had been temporarily relieved by injections of salvarsan. Treatment with salvarsan was soon followed by numbness over the abdomen and a dragging sensation in the perineum and by incontinence of urine. These symptoms were relieved by four injections of salvarsanized serum intraspinally. At entrance to the hospital he complained of numbness in the fingers of the left hand, numbness and loss of sensation on the left side of the abdomen, girdle sensation, loss of sexual power, sensation of walking on cotton and inability to run and jump.

Physical examination showed that the pupils reacted slightly to light and that the deep reflexes of the arms and legs were absent. The Romberg test was slightly positive. The Wassermann reaction in the blood serum was negative, in the spinal fluid it was positive with 0.6 c.c. The spinal fluid cell count was 3.

On October 31, November 21 and December 12, respectively, three intraspinal injections of salvarsanized serum were given. The numbness and the sensation of walking on cotton were relieved and the spinal fluid showed 3 cells per c.mm. and a positive Wassermann reaction with 0.8 c.c. On January 9 a fourth treatment relieved the girdle sensation and on February 6 a fifth treatment showed the spinal fluid cell count to be 1, sexual power had returned and the patient felt well. On March 20 a sixth treatment was given and the spinal

fluid was negative with 1 c.c., but the blood serum, which had been found to be negative previously, on this date gave a positive reaction, so that the patient was given six doses of salvarsan intravenously. At the expiration of four months the patient was free from symptoms and the spinal fluid gave a negative reaction with 1 c.c. but as the blood was still positive further treatment with salvarsan was given.

CASE 34.—A man, aged 35, entered the hospital Jan. 14, 1915. A diagnosis of tabes dorsalis was made. He had had rheumatic pains in the joints for several years. During the year previous to entrance he had become very nervous and irritable. For the previous six months he had had paroxysmal pain in the right side and sharp, stabbing pains in the thighs and knees and pains encircling the waist. For the past few weeks he had had dizziness and increasing unsteadiness in the gait, more noticeable in the dark.

Physical examination showed that the pupils reacted slightly to light, that the deep arm reflexes were hyperactive and that the deep leg reflexes were absent; the Romberg test was positive with marked staggering. The Wassermann reaction in the blood serum was negative, in the spinal fluid it was positive with 0.1 c.c. and there were 88 cells per c.mm.

On January 26 the first intraspinal treatment relieved the girdle sensation. On February 2 the second treatment relieved the dizziness and diminished the intensity of the pains; the spinal fluid cell count was reduced to 26. On February 9 the third treatment entirely relieved the pain, and the patient was able to walk more steadily. On February 16, February 24 and March 9, respectively, the fourth, fifth and sixth treatments were given. The patient was entirely free from symptoms and the spinal fluid showed 3 cells and a positive Wassermann reaction with 0.3 c.c. On March 23 the seventh treatment produced a bad reaction, with headache and vomiting for several days. On April 13 he was free from symptoms, the cell count was 3 and an eighth treatment was given. On June 15, July 10 and September 25, respectively, the ninth, tenth and eleventh treatments were given. During this time the spinal fluid showed a cell count varying between 2 and 4 and the Wassermann reaction was positive with 0.4 c.c.

All pains, nervousness, mental depression and lassitude were entirely relieved and there was no ataxia except on sudden turning. Six months have elapsed since the last treatment, without any return of symptoms and the patient has been able to work for the past eight months.

CASE 35.—A man, aged 36, entered the hospital Feb. 9, 1915. A diagnosis of cerebrospinal syphilis was made. He had a chancre twenty years before and had been treated with mercury by mouth and by inunctions for one year. During the previous eight years he had been treated with potassium iodid by mouth and with corrosive sublimate by injections. Two months previous to entrance he had noticed marked sleepiness and a whirling before the eyes. For the previous three weeks he had had a constant dull headache. Two days previous to admission he had had a sudden attack of unconsciousness lasting all night and this was followed by diplopia.

Physical examination showed that both pupils did not react to light; that there was a slight nystagmus and internal strabismus. All deep arm and leg reflexes were very active. The patient slept all the time. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.2 c.c. The spinal fluid cell count was 83.

On February 13 the spinal fluid showed 100 cells per c.mm. and the first treatment was given. On February 15 the cells were 150 per c.mm. and the second treatment was given. On February 21 the third treatment was given and the spinal fluid cell count was reduced to 75 and the headache, diplopia, and external rectus weakness disappeared. On March 2 the fourth treatment was given; the cells became 27 and the patient was practically free from symptoms, being only a little drowsy and sleeping little during the day. On March

24 the fifth treatment was given. The spinal fluid cell count was 12 per c.mm. and the patient was free from all symptoms and was discharged. Ten months have elapsed since treatment was stopped and he has worked every day.

CASE 38.—A man, aged 37, entered the hospital May 3, 1915. A diagnosis of tabes dorsalis was made. He had had a chancre eighteen years before. For the previous two years he had had shooting pains in the legs, and during the last year before entrance he had had transient diplopia, and for the previous seven months ataxia, disturbances in micturition, girdle pains and lightning pains in the legs. For the previous eight days he had had vomiting after the taking of food and hiccuping constantly at the rate of 20 to 30 per minute.

Physical examination showed the pupils to be unequal and inactive to light. All deep reflexes were absent and the Romberg test was markedly positive. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.3 c.c. The spinal fluid cell count was 63 per c.mm.

Large doses of morphin had no influence on the hiccup, which was present during sleep. On May 12 the first intraspinal treatment was given and the vomiting and hiccup were relieved after a few hours. The spinal fluid cell count increased to 103 per c.mm. On May 20 a second treatment was given, the spinal fluid cell count became 48 per c.mm. and the pains, vomiting and hiccup ceased. On May 29, June 3, June 24, and July 25 treatments were given; the spinal fluid cell count dropped to 15 per c.mm. and the patient remained free from all symptoms. On August 5 the hiccup began again and was again relieved in a few hours. On August 23, after a period of five days of hiccuping the eighth treatment was given and the hiccup again disappeared. At this time the spinal fluid showed 6 cells and a negative Wassermann reaction with 1 c.c.

Eight intraspinal treatments changed the Wassermann reaction in the spinal fluid from 0.3 c.c. positive to 1 c.c. negative and changed the spinal fluid cell count from 103 per c.mm. to normal. The treatments temporarily relieved the hiccup on three successive occasions and finally relieved it permanently. The treatments also relieved the pain and vomiting and the ataxia was greatly improved.

CASE 42.—A boy, aged 3½ years, entered the hospital May 10, 1915. A diagnosis of syphilitic meningitis was made. For the previous six months he had had pain in the right ear. For the previous six weeks he had had periodic severe headaches accompanied by projectile vomiting, retraction of neck, fever and loss of weight. Lumbar puncture revealed no organisms and antimeni-gococcic serum was given without relief. On two successive days lumbar puncture revealed a turbid fluid, but no organisms were found in smears or cultures. On the next day, May 10, he was admitted to this hospital with opisthotonus, a rigid neck, positive Kernig sign, a temperature of 104 and a pulse of 150 per minute. Lumbar puncture revealed a turbid spinal fluid, showing 9,800 cells per c.mm. (62 per cent. lymphocytes, 26 per cent. polymorphonuclears, 12 per cent. endothelial cells), no organisms and a positive Wassermann reaction with 0.1 c.c. The Wassermann reaction in the blood serum was positive.

An intravenous injection of 0.2 gm. salvarsan gave no relief. A few days later, on May 22, the first intraspinal treatment was given and this relieved the opisthotonus, the temperature was reduced to 101 and the spinal fluid cell count was reduced to 7,300 per c.mm. On May 24 a second intraspinal treatment relieved the stiffness of the neck, the positive Kernig sign disappeared, and the spinal fluid cell count was reduced to 2,500. On May 27 the third intraspinal treatment was given, the child appeared normal in every way; the spinal fluid cell count was 126 per c.mm. and the Wassermann reaction was positive with 0.2 c.c. On May 29 0.2 gm. of salvarsan was given; on June 3 a fourth intraspinal treatment was given and the child was discharged apparently well. On June 10, July 1 and July 15, respectively, the fifth, sixth and seventh intraspinal treatments were given. At the end of this time the spinal fluid showed

a normal cell count and a negative Wassermann reaction with 2 c.c. Each treatment consisted of 20 c.c. of undiluted salvarsanized serum. The Wassermann reaction in the blood serum also became negative.

No benefit resulted from repeated lumbar puncture, from the injection of antimeningococcic serum or from the first dose of salvarsan; but the first intraspinal treatment with salvarsanized serum relieved the opisthotonus and reduced the spinal fluid cell count from 9,800 to 7,300, and a second similar treatment relieved all symptoms and further reduced the cell count to 2,500 per c.mm. Nine months have elapsed since treatment was stopped and no return of symptoms have developed. It is quite remarkable that seven intraspinal treatments should accomplish so much. The age of the patient (3½ years), the similarity to tuberculosis meningitis, and the negative Wassermann reaction in both parents add considerable interest to the case.

CASE 66.—A man, aged 41, entered the hospital Dec. 10, 1915. A diagnosis of *tabes dorsalis* was made. For the previous two years he had had shooting pains and hyperesthesia in the legs. Three weeks before he had had a sudden attack of vertigo and ataxia, both of which passed away in a few months. For the previous week he had had pains in the joints and vomiting.

Physical examination showed that the pupils reacted sluggishly to light; the left was larger than the right. The right knee jerk was absent and the left was hyperactive. There was some ataxia. The Wassermann reaction in the blood serum was negative and in the spinal fluid it was positive with 0.3 c.c. The spinal fluid cell count was 29 per c.mm.

Four intraspinal treatments with salvarsanized serum were given at weekly intervals.

The pains, vertigo and hyperesthesia were relieved and the ataxia was decreased.

NOTE.—All treatments were given and all the laboratory work was done by the authors.

A NOTE ON THE BLOOD FAT BEFORE AND AFTER SPLENECTOMY*

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Recently, King¹ and Eppinger² found that the removal of the spleen resulted in an increase in total fats and lipoids, an increase in cholesterol, and a decrease in the unsaturated fatty acids, as expressed by the iodine number. In addition there was found in severe anemias a very high iodine number, suggesting that hemolysis in anemia is in some way related to the unsaturated fatty acids.

TABLE 1.—BLOOD FAT BEFORE AND AFTER SPLENECTOMY*

Dog	Before Splenectomy		Ten Days after Splenectomy		Remarks
	Total Fats, Gm.	Iodine Number	Total Fats, Gm.	Iodine Number	
15-53 Serum.....	2.6	51.6	2.82†	51.5	} Blood drawn into oxalate
Cells.....	2.93	43.7	2.42	52	
15-67 Serum.....	2.85†	51.6	2.83†	51.5	} Blood drawn into oxalate
Cells.....	2.43	53.4	2.43	49.4	
15-76.....	5.63	47.6	5.99	47	Blood drawn into alcohol
15-75.....	5.25	49	5.53	48.2	Blood drawn into alcohol
16-23.....	5.73	47.4	6.036	49.6	Blood defibrinated
16-4.....	7.6	70.1	7.71	65	Blood defibrinated

* The iodine number is calculated on the basis of the total amount of fatty extract found in 100 c.c. of blood; the total fats are calculated per 1,000 c.c. of blood.

† As some hemolysis took place while separating the cells from the serum, there may be some inaccuracy in the relative values given for cells and serum.

As a preliminary step to other investigations of the blood fats which we had in mind, it was thought advisable to repeat some of the work of King and Eppinger, that is, that dealing with the total fats and unsaturated fatty acids. King's technic was followed, except that cholesterol and cholesterol esters were not removed before determining the iodine number. We do not believe, however, that our failure to

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1. King, J. H.: Studies in the Pathology of the Spleen, THE ARCHIVES INT. MED., 1914, xiv, 145.

2. Eppinger, H.: Zur Pathologie der Milzfunktion, Berl. klin. Wchnschr., 1913, 1, 1509.

obtain results in accord with those of King and Eppinger can be explained by this difference in method. Our results are summarized in Table 1.

An examination of the figures in Table 1 reveals the fact that the total fats and the iodine number are practically the same both before and after splenectomy, whereas King and Eppinger report under similar conditions a marked increase in total fats, together with an equally definite decrease in the unsaturated fatty acids, as expressed by the iodine number.

SUMMARY

Analysis, before and after splenectomy, of the blood of dogs shows practically no change in the amount of total fats and unsaturated fatty acids, as expressed by the iodine value.

BOOK REVIEW

THE PHYSIOLOGY OF THE AMINO-ACIDS. By Frank P. Underhill, Ph.D., Professor of Pathological Chemistry, Yale University, New Haven: Yale University Press. Price, \$1.35 net.

In his preface the author very justly emphasizes the urgent need for a book or monograph on this subject. He has written a summary for the "busy practitioner and others whose resources for consulting original communications are limited." Professor Underhill has carefully analyzed the existing literature and has produced a work which, in a very concise but thorough manner, brings out the most important facts concerning the proteins and amino-acids. The successive chapters deal with the derivation of amino-acids from proteins, the digestion, absorption and excretion of the amino-acids, and their relation to the organism in health and disease. The mere lists of amino-acids and their formulas and other matter which it is a question of "mental gymnastics" to memorize and which serve for necessary reference only are quickly disposed of, and the following chapters on the physiologic and pathologic chemistry of these substances unfold themselves in logical sequence. The treatment of the subject is that of the finished lecturer, thoroughly conversant with his subject, expounding it to a class of beginners. This is a very excellent method of presentation. For the clinician the book gives an adequate exposition of the scientific aspect of the subject, but is not far-reaching enough on its clinical side. The subjects of intestinal putrefaction, auto-intoxication, acidosis, elimination and retention of the end-products of protein metabolism, protein feeding in disease, etc., are not taken up from the physician's point of view. There are clinicians broad enough to be interested in these subjects quite apart from their immediate practical value in the treatment of disease, but they are very few in number. The majority of medical men naturally desire to have the laboratory worker show them how they may apply the "test tube" knowledge to their patients. For the most part a dead line exists between the activities of scientific and clinical workers, which only few individuals from either side are capable of crossing. Professor Underhill has not succeeded in crossing it. The consequence is that while his book presents a very satisfactory though brief review of the amino-acids and proteins from the point of view of the physiologic and pathologic chemist, it does not cover the relations of these substances to clinical problems in as thorough a manner as might be desired.

There are a moderate number of misprints in this volume. One of the most disconcerting is in the formula for dextrose, given as $C_6H_6O_6$ four times within two pages (pages 111 and 112).

There is a great need for essays on this and kindred subjects for physicians. Professor Underhill's little book may be said to be a pioneer in this direction. However, to disseminate knowledge to large numbers of practitioners, it is believed that more attention must be paid to its clinical application.

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RENAL FUNCTION IN PERNICIOUS ANEMIA

AS DETERMINED BY DIETARY RENAL TESTS *

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In 1914 Hedinger and Schlayer¹ described a dietary test for renal function which consisted in estimating the amount of urine, its specific gravity, and its content in sodium chlorid and nitrogen, both the total amount and percentage concentration in two hour specimens collected throughout the day and in a single night specimen. Their patients were placed on a special diet so arranged that different meals given throughout the day should have varying amounts of fluids, sodium chlorid, protein and purin bases. Slight modifications of these diets will be found in the papers published by Mosenthal² from the Johns Hopkins Hospital Clinic, and O'Hare³ from the Peter Bent Brigham Hospital Clinic.

A normal person under the conditions of such a diet shows variations in all of the factors determined in the test in relation to the meals, so that when the results of the test are charted the columns and lines form an irregular or picket fence curve (Fig. 1, P. B. B. H. Med. No. 3337). In cases of nephritis these curves are flattened out toward straight lines in relation to the character and severity of the renal involvement (Fig. 2, P. B. B. H. Med. No. 2567). Mosenthal² mentions that in patients with severe anemia results were obtained with the test diet which are similar in every detail to those found in advanced cases of contracted kidney. Similar conditions he finds in patients with prostatic hypertrophy, pyelonephritis and polycystic kidney. In these

* Submitted for publication July 3, 1916.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

* Read by title at a meeting of the American Society for the Advancement of Clinical Investigation, held in Washington, D. C., May 8, 1916.

1. Hedinger and Schlayer: *Deutsch. Arch. f. klin. Med.*, 1914, cxiv, 120.

2. Mosenthal: *THE ARCHIVES INT. MED.*, 1915, xvi, 733.

3. O'Hare: *THE ARCHIVES INT. MED.*, 1916, xvii, 711.

latter it would seem that pathological conditions simulate closely those found in chronic nephritis, whereas in severe anemia it would not be probable that the kidney had undergone a change in any way analogous to the changes of chronic nephritis. Mosenthal⁴ gives one chart of a patient with anemia in which the hemoglobin was 44 per cent. and the red blood cells 2,240,000, but he gives no further details as to the patient's condition. It seemed interesting in view of this report of

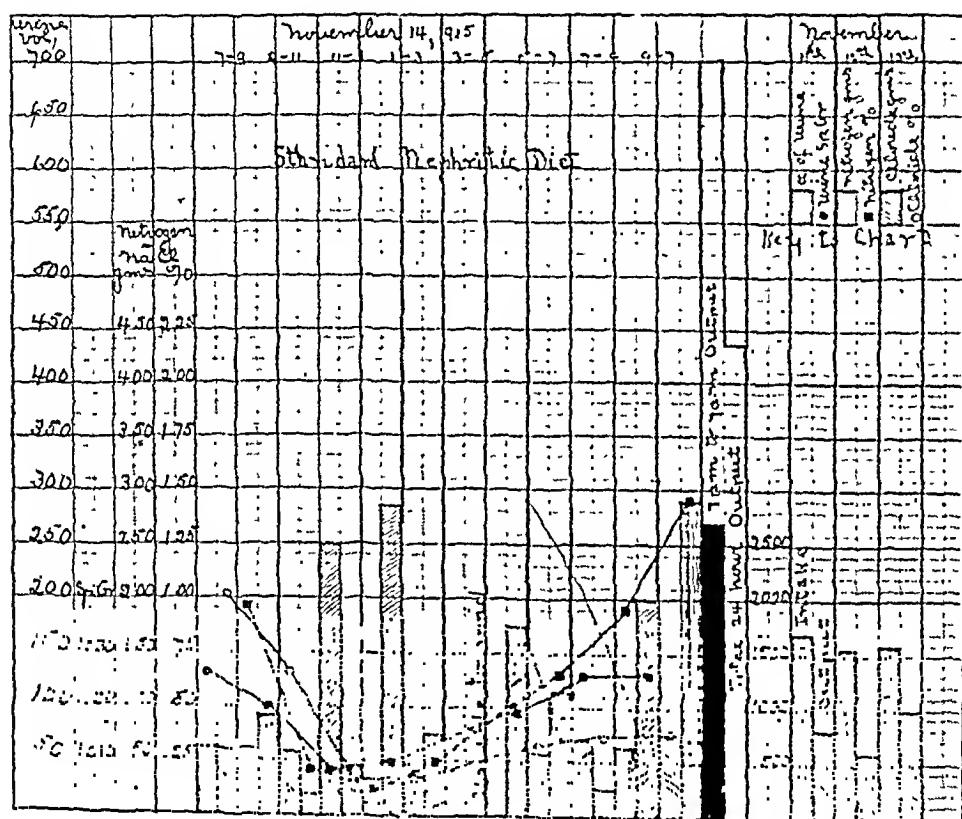


Fig. 1 (P. B. B. H., Med. No. 3337).—Diagnosis, mitral insufficiency and regurgitation; chronic myocarditis. The heart at time of the test was well compensated. In this and the following three illustrations, the series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in every two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the twenty-four-hour fluid intake and urine output in the days preceding the test day.

4. Mosenthal in a recent paper before the medical section of the American Medical Association, held in Detroit, June 13-15, 1916, has given a further discussion of these changes in renal function in cases of severe anemia and outlined the results of examination of several cases.

TABLE 1.—TWO-HOUR RENAL TEST IN CASE 1, MADE MARCH 24, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	119	1.019	0.58	0.69	0.30	0.36
9 to 11.....						
11 to 1.....	122	1.018	0.65	0.79	0.30	0.37
1 to 3.....	123	1.018	0.75	0.92	0.29	0.36
3 to 5.....	122	1.017	0.61	0.74	0.28	0.34
5 to 7.....	138	1.016	0.60	0.83	0.25	0.35
7 to 9.....	149	1.017	0.60	0.89	0.21	0.31
9 to 7.....	410	1.019	0.71	2.91	0.25	1.03
Total.....	1,183	7.77	3.12

A blood test April 9, in Case 1 showed hemoglobin 19 per cent., and red blood corpuscles 970,000; and on April 12, hemoglobin 16 per cent., and red blood corpuscles 920,000.

The urine on April 10 showed no albumin and no casts.

On April 8 transfusion of 300 c.c. blood was made.

TABLE 2.—TWO-HOUR RENAL TEST IN CASE 1, MADE APRIL 11, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	123	1.016	0.46	0.57	0.52	0.64
9 to 11.....	160	1.015	0.37	0.59	0.54	0.86
11 to 1.....	92	1.016	0.48	0.44	0.58	0.58
1 to 3.....	153	1.015	0.40	0.61	0.54	0.83
3 to 5.....	150	1.014	0.41	0.62	0.50	0.75
5 to 7.....	71	1.016	0.54	0.38	0.48	0.34
7 to 9.....	135	1.014	0.60	0.81	0.46	0.62
9 to 7.....	475	1.014	0.48	2.28	0.44	2.09
Total.....	1,359	6.30	6.66

On April 12 blood test showed hemoglobin 16 per cent., red blood corpuscles 970,000; on April 14, hemoglobin 35 per cent., red blood corpuscles 1,320,000.

On April 12 a transfusion of 600 c.c. blood was made.

TABLE 3.—TWO-HOUR RENAL TEST IN CASE 1, MADE APRIL 14, 1916 *

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	245	1.015	0.32	0.78	0.86	2.11
9 to 11.....	92	1.019	0.23	0.21	0.99	0.90
11 to 1.....	86	1.020	0.54	0.46	0.98	0.84
1 to 3.....	117	1.019	0.48	0.56	0.91	1.07
3 to 5.....	135	1.017	0.55	0.74	0.76	1.03
5 to 7.....	125	1.018	0.54	0.68	0.79	0.99
7 to 9.....	215	1.016	0.38	0.82	0.68	1.86
9 to 7.....	400	0.38	0.82	0.68	1.86
Total.....	1,415	4.04+	8.80+

* In the table of April 14, in contrast to that of April 11, there is a slightly less marked fixation in curves of excretion along with the moderately improved blood condition following transfusion.

CASE 2 (P. B. B. H. Med. No. 4181).—A man, aged 51 years, was given a blood test April 11, and showed hemoglobin 42 per cent., red blood corpuscles 1,960,000.

The phenolsulphonaphthalein excretion on April 5 was 66 per cent. in two and one-quarter hours. The urine on April 8, showed no albumin and no casts.

On February 29 a transfusion of 550 c.c. blood was made. On April 6 diarsenol was given intravenously, 0.2 gm., and on April 9 another transfusion of 375 c.c. blood was made.

TABLE 4.—TWO-HOUR RENAL TEST IN CASE 2, MADE APRIL 11, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	48	1.026	0.78	0.37	1.28	0.61
9 to 11.....	75	1.025	1.07	0.80	0.96	0.72
11 to 1.....	64	1.024	0.95	0.61	0.99	0.63
1 to 3.....	74	1.024	1.04	0.77	0.98	0.73
3 to 5.....	100	1.024	0.82	0.82	0.98	0.98
5 to 7.....	98	1.025	0.70	0.69	0.98	0.96
7 to 9.....	87	1.023	0.85	0.74	0.97	0.87
9 to 7.....	448	1.019	0.56	2.51	0.98	4.39
Total.....	994	7.31	9.89

Blood examination in Case 2, made April 27, showed hemoglobin 80 per cent., red blood corpuscles 3,460,000; and on May 4, hemoglobin 82 per cent., red blood corpuscles 3,500,000.

The urine April 28, showed no albumin or casts.

On April 18, diarsenol was given intravenously, 0.2 gm.

TABLE 5.—TWO-HOUR RENAL TEST IN CASE 2, MADE MAY 3, 1916 *

Time	Volume. C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	76	1.022	0.63	0.48	1.26	0.96
9 to 11.....	67	1.024	0.61	0.43	1.23	0.82
11 to 1.....	130	1.019	0.50	0.65	0.99	1.29
1 to 3.....	104	1.024	0.73	0.76	1.07	1.11
3 to 5.....	128	1.022	0.61	0.82	1.16	1.49
5 to 7.....	56	1.028	0.92	0.52	1.28	0.72
7 to 9.....	74	1.027	0.90	0.67	1.26	0.93
9 to 7.....	603	1.017	0.56	3.38	0.88	5.31
Total.....	1,238	7.71	12.63

* These two observations on the same case show evidence of a return toward normality in renal excretion with improved blood condition.

CASE 3 (P. B. B. H., Med. No. 4292).—A woman, aged 28 years, was given a blood examination April 13, which showed hemoglobin 37 per cent., red blood corpuscles 1,230,000. The phenolsulphonephthalein excretion on April 13 was 36 per cent. in two hours.

The urine on April 8 showed the slightest possible trace of albumin, but large numbers of hyaline and finely granular casts, and an occasional coarsely granular cast.

The treatment from March 9 to March 17, was Fowler's solution and hydrochloric acid. On March 15 transfusion of 500 c.c. blood was made, and on April 10 diarsenol, 0.2 gm., was given intravenously.

TABLE 6.—TWO-HOUR RENAL TEST IN CASE 3, MADE APRIL 17, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	200	1.012	0.24	0.48	0.52	1.04
9 to 11.....	660	1.007	0.03	0.20	0.19	1.25
11 to 1.....						
1 to 3.....	205	1.012	0.13	0.27	0.47	0.96
3 to 5.....	380	1.011	0.06	0.23	0.38	1.44
5 to 7.....	Unable to void					
7 to 9.....						
9 to 7.....						
Total.....	1,445	1.18	4.69

Blood test made April 25 showed hemoglobin 61 per cent., red blood corpuscles 1,780,000, and on April 29, hemoglobin 76 per cent., red blood corpuscles 1,840,000.

The treatment from April 24 to April 26 was Fowler's solution, and on April 26 diarsenol was given intravenously, 0.2 gm.

TABLE 7.—TWO-HOUR RENAL TEST IN CASE 3, MADE APRIL 26, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	245	1.014	0.38	0.69	0.63	1.54
9 to 11.....	275	1.008	0.15	0.41	0.27	0.64
11 to 1.....	240	1.007	0.13	0.31	0.27	0.65
1 to 3.....	180	1.012	0.15	0.27	0.56	1.01
3 to 5.....	310	1.008	0.14	0.43	0.38	1.18
5 to 7.....	250	1.010	0.22	0.55	0.52	1.30
7 to 9.....	185	1.013	0.11	0.20	0.51	0.92
9 to 7.....						
Total.....	1,685	2.86	7.24

CASE 4 (P. B. B. H., Med. No. 4316).—A woman, aged 48, was given a blood examination March 13, which showed hemoglobin 52 per cent., red blood corpuscles 1,720,000; and on March 20, hemoglobin 54 per cent., red blood corpuscles 1,810,000. The phenolsulphonephthalein excretion on April 7 was 57 per cent. in two hours.

The urine on March 15 showed very slight trace of albumin and few hyaline and granular casts. On April 4 there was the slightest possible trace of albumin with an occasional hyaline and granular cast.

The treatment was Fowler's solution March 14 to March 23.

TABLE 8.—TWO-HOUR RENAL TEST IN CASE 4, MADE MARCH 16, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	56	1.019	0.46	0.26	0.44	0.25
9 to 11.....	120	1.018	0.74	0.89	0.30	0.36
11 to 1.....						
1 to 3.....	160	1.020	0.73	1.17	0.36	0.58
3 to 5.....						
5 to 7.....	60	1.019	0.77	0.46	0.36	0.22
7 to 9.....	307	1.020	0.42	1.29	0.34	1.04
9 to 7.....						
Total.....	703	4.07	2.45

CASE 5 (P. B. B. H., Med. No. 4404).—A woman, aged 60, was given a blood examination March 27, which showed hemoglobin 30 per cent., red blood corpuscles 1,440,000; and on April 3, hemoglobin 34 per cent., red blood corpuscles 1,430,000. The phenolsulphonephthalein excretion on April 7 was 55 per cent. in two hours.

The urine on March 29 showed the slightest possible trace of albumin and few hyaline and granular casts. On April 8 there was the slightest possible trace of albumin with an occasional hyaline and granular cast.

The treatment was Fowler's solution from March 28 to April 10.

TABLE 9.—TWO-HOUR RENAL TEST IN CASE 5, MADE MARCH 31, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	140	1.016	0.74	1.05	0.42	0.50
9 to 11.....	33	1.016	0.44	0.15	0.38	0.13
11 to 1.....	134	1.017	0.71	0.95	0.38	0.51
1 to 3.....						
3 to 5.....	46	1.018	0.38	0.17	0.31	0.16
5 to 7.....	73	1.015	0.71	0.52	0.40	0.22
7 to 9.....	56	1.016	0.71	0.40	0.31	0.17
9 to 7.....						
Total.....	482	3.24	1.85

CASE 6 (P. B. B. H., Med. No. 4217).—A woman, aged 60, was given a blood examination March 10, which showed hemoglobin 26 per cent., red blood corpuscles 790,000; and on March 17, hemoglobin 26 per cent., red blood corpuscles 750,000. The phenolsulphonephthalein excretion on March 7 was 36 per cent. in two hours.

The urine on March 16 showed very slight trace of albumin with an occasional hyaline and granular cast.

This patient had had splenectomy several months before with but little resultant change in the blood picture. Later there had been a decline in the blood condition.

TABLE 10.—TWO-HOUR RENAL TEST IN CASE 6, MADE MARCH 15, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	39	1.016	0.64	0.25	0.28	0.11
9 to 11.....	36	1.016	0.72	0.26	0.28	0.10
11 to 1.....	101	1.014	0.60	0.70	0.28	0.28
1 to 3.....	78	1.014	0.35	0.27	0.20	0.23
3 to 5.....	102	1.014	0.52	0.53	0.29	0.30
5 to 7.....						
7 to 9.....	20	1.018	0.17	0.03	0.33	0.07
9 to 7.....	400	1.014	0.64	2.56	0.36	1.44
Total.....	776	4.60	2.53

CASE 7 (P. B. B. H., Med. No. 4505).—A man, aged 47, was given a blood examination April 13, which showed hemoglobin 45 per cent., red blood corpuscles 1,970,000; on April 18, hemoglobin 48 per cent., red blood corpuscles

1,300,000; and on April 25, hemoglobin 49 per cent., red blood corpuscles 1,420,000. The phenolsulphonephthalein excretion on April 14 was 67 per cent. in two hours.

The urine on April 15 showed no albumin and the sediment was negative. The same condition existed on April 25.

TABLE 11.—TWO-HOUR RENAL TEST IN CASE 7, MADE APRIL 18, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	45	1.024	0.73	0.33	0.22	0.10
9 to 11.....	95	1.021	1.07	1.02	0.44	0.42
11 to 1.....	87	1.024	1.03	0.90	0.66	0.57
1 to 3.....	66	1.024	1.15	0.76	0.63	0.42
3 to 5.....	165	1.022	0.79	1.30	0.78	1.29
5 to 7.....	110	1.023	0.68	0.75	0.96	1.06
7 to 9.....	66	1.023	0.99	0.65	0.52	0.34
9 to 7.....	150	1.023	1.12	1.68	0.72	1.08
Total.....	784	7.39	5.28

CASE 8 (P. B. B. H., Med. No. 4064).—A man, aged 63 years, was given a blood examination March 17, which showed hemoglobin 35 per cent., red blood corpuscles 1,520,000; and on March 26, hemoglobin 41 per cent., red blood corpuscles 1,728,000. The phenolsulphonephthalein excretion on April 5 was 38 per cent. in two and one-quarter hours.

The urine on March 23 showed the slightest possible trace of albumin and no casts. The same condition was shown on April 3.

The treatment from January 30 to February 5 was Fowler's solution. On February 12 diarsenol, 0.3 gm. was given intravenously. The same amount was given on February 26, and on March 8 a transfusion of 750 c.c. of blood was made.

TABLE 12.—TWO-HOUR RENAL TEST IN CASE 8, MADE MARCH 23, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	107	1.020	0.47	0.50	1.02	1.09
9 to 11.....	75	1.022	0.62	0.47	0.91	0.68
11 to 1.....	74	1.021	0.51	0.38	0.95	0.70
1 to 3.....	100	1.021	0.60	0.60	0.94	0.94
3 to 5.....	90	1.022	0.40	0.36	1.13	1.02
5 to 7.....	76	1.021	0.50	0.38	0.90	0.68
7 to 9.....	92	1.021	0.43	0.40	0.79	0.73
9 to 7.....	409	1.019	0.36	1.47	1.02	4.17
Total.....	1,023	4.56	9.01

Another blood examination was made April 11, which showed hemoglobin 43 per cent., red blood corpuscles 1,510,000; and on April 18, hemoglobin 47 per cent., red blood corpuscles 1,700,000.

The urine on April 18 showed no albumin and no casts.

TABLE 13.—TWO-HOUR RENAL TEST IN CASE 8, MADE APRIL 16, 1916 *

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	180	1.020	0.63	1.13	1.03	1.85
9 to 11.....	105	1.022	0.73	0.77	0.93	0.95
11 to 1.....	188	1.021	0.61	1.15	0.97	1.82
1 to 3.....	92	1.022	0.68	0.65	0.97	0.89
3 to 5.....	113	1.022	0.60	0.68	0.99	1.23
5 to 7.....	97	1.022	0.65	0.63	1.05	1.02
7 to 9.....	125	1.020	0.56	0.70	0.89	1.11
9 to 7.....	515	1.020	0.58	2.90	1.08	5.56
Total.....	1,415	8.70	14.46

* Here the two observations are practically identical and the blood at each observation showed almost the same condition.

CASE 9 (P. B. B. H., Med. No. 4609).—A man, aged 73, was given a blood examination May 4, which showed hemoglobin 29 per cent., red blood corpuscles 1,090,000; and on May 8, hemoglobin 31 per cent., red blood corpuscles 1,020,000. The phenolsulphonephthalein excretion on May 8 was 34 per cent. in two hours.

The urine on May 6, showed no albumin, but an occasional hyaline cast. On May 25 there was no albumin, but many leukocytes and epithelial cells.

TABLE 14.—TWO-HOUR RENAL TEST IN CASE 9, MADE MAY 7, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	64	1.013	0.43	0.28	0.76	0.49
9 to 11.....	205	1.013	0.29	0.60	0.67	1.37
11 to 1.....	355	1.012	0.25	0.89	0.70	2.49
1 to 3.....						
3 to 5.....						
5 to 6:30.....	300	1.009	0.22	0.66	0.84	1.02
6:30 to 9.....						
9 to 7.....	435	1.012	0.23	1.00	0.59	2.56
Total.....	1,359	3.43	..	7.98

CASE 10 (P. B. B. H., Med. No. 4694).—A man, aged 63, was given a blood examination, May 18, which showed hemoglobin 35 per cent., red blood corpuscles 1,280,000; and on May 25, hemoglobin 34 per cent., red blood corpuscles 1,360,000. The phenolsulphonephthalein excretion on May 22 was 54 per cent. in two hours.

The urine on May 20, showed the slightest possible trace of albumin, with an occasional epithelial cell, hyaline cell and finely granular cast.

The treatment from May 19 to June 6 was dilute hydrochloric acid, given three times a day. On May 24, diarsenol, 0.3 gm., was given intravenously.

TABLE 15.—TWO-HOUR RENAL TEST IN CASE 10, MADE MAY 24, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	59	1.018	0.73	0.43	0.52	0.31
9 to 11.....	79	1.018	0.55	0.42	0.56	0.43
11 to 1.....	95	1.017	0.63	0.60	0.63	0.60
1 to 3.....	74	1.018	0.74	0.55	0.59	0.44
3 to 5.....	53	1.019	0.76	0.40	0.47	0.25
5 to 7.....	77	1.018	0.83	0.64	0.44	0.34
7 to 9.....	73	1.017	0.72	0.52	0.40	0.29
9 to 7.....	213	1.017	0.73	1.56	0.38	0.81
Total.....	720	5.12	3.47

CASE 11 (P. B. B. H., Med. No. 4478).—A woman, aged 38, was given a blood examination April 8, which showed hemoglobin 28 per cent., red blood corpuscles 1,140,000. The phenolsulphonephthalein excretion on April 10, was 60 per cent. in two hours.

The urine on April 10 showed the slightest possible trace of albumin with an occasional hyaline and finely granular cast.

The treatment was dilute hydrochloric acid, 1 c.c. three times a day from April 8 to May 1.

TABLE 16.—TWO-HOUR RENAL TEST IN CASE 11, MADE APRIL 12, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	39	1.018	0.84	0.33	0.40	0.16
9 to 11.....	48	1.016	0.74	0.26	0.28	0.15
11 to 1.....	135	1.012	0.68	0.92	0.34	0.46
1 to 3.....						
3 to 5.....	82	1.012	0.71	0.58	0.24	0.20
5 to 7.....	175	1.009	0.42	0.74	0.18	0.32
7 to 9.....	101	1.013	0.52	0.53	0.28	0.28
9 to 7.....	453	1.013	0.44	1.99	0.30	1.36
Total.....	1,033	5.35	2.93

CASE 12 (P. B. B. H., Med. No. 4748).—A man, aged 42 years, was given a blood examination June 3, which showed hemoglobin 34 per cent., red blood

corpuscles 1,330,000; and on June 9, hemoglobin 40 per cent., red blood corpuscles 1,560,000. The phenolsulphonephthalein excretion on May 30 was 45 per cent. in two hours.

The urine on May 30 showed no albumin, with occasional epithelial cell, but no casts. The same condition existed June 9.

On June 8, 375 c.c. citrated blood was given intravenously.

TABLE 17.—TWO-HOUR RENAL TEST IN CASE 12, MADE JUNE 8, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	66	1.015	0.57	0.23	0.59	0.23
9 to 11.....	123	1.017	0.69	0.86	0.49	0.59
11 to 1.....						
1 to 3.....	138	1.015	0.52	0.72	0.42	0.53
3 to 5.....	379	1.007	0.15	0.65	0.09	0.31
5 to 7.....	204	1.006	0.06	0.12	0.05	0.16
7 to 9.....						
9 to 7.....	250	1.012	0.65	1.70	0.07	0.18
Total.....	1,162	4.46	2.09

CASE 13 (P. B. B. H., Med. No. 4565).—A woman, aged 38 years, was given a blood examination April 26, which showed hemoglobin 19 per cent., red blood corpuscles 460,000. The phenolsulphonephthalein excretion on April 28 was 24 per cent. in two hours.

The urine on April 28, showed no albumin, but a few squamous cells. There was no albumin again on May 25, but an occasional coarsely granular cast and epithelial cell.

The treatment was dilute hydrochloric acid, 1 c.c. three times a day from April 26 to May 10.

TABLE 18.—TWO-HOUR RENAL TEST IN CASE 13, MADE APRIL 27, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9 } Unable to void	515	1.012	0.50	2.58	0.02	0.10
9 to 11 }						
2 a. m. to 12:20.....						
12:20 to 3 Unable to void	310	1.012	0.46	1.43	0.01	0.12
3 to 5.....						
5 to 7 } Unable to void						
7 to 9 }	160 at 5 p. m. lost					
9 to 7.....						
Total.....	985	4.01+	0.22+

Another blood examination was made April 30, which showed hemoglobin 19 per cent., red blood corpuscles 710,000.

TABLE 19.—TWO-HOUR RENAL TEST IN CASE 13, MADE APRIL 30, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	15	0.72	0.11	0.06	0.01
9 to 11.....						
11 to 1.....	405	1.012	0.55	2.24	0.03	0.12
1 to 3.....						
3 to 5.....	360	1.012	0.58	1.93	0.03	0.10
5 to 7.....						
7 to 8.....	280	1.012	0.47	1.29	0.47	1.29
8 to 7.....						
Total.....	1,060	5.57	1.52

Further examination of the blood on June 3, showed hemoglobin 74 per cent., red blood corpuscles 2,510,000; and on June 11, hemoglobin 70 per cent., red blood corpuscles 2,740,000.

The urine on June 4 showed no albumin, but many epithelial cells and leucocytes, with rarely a coarsely granular cast. On June 15 there was no albumin but some epithelial cells.

On May 6 a transfusion of 600 c.c. of blood was made; also 500 c.c. on May 7, and on May 23, 600 c.c. citrated blood were injected.

TABLE 20.—TWO-HOUR RENAL TEST IN CASE 13, MADE JUNE 8, 1916*

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	170	1.010	0.27	0.46	0.52	0.88
9 to 11.....	82	1.014	0.43	0.35	0.72	0.59
11 to 1.....	340	1.007	0.13	0.44	0.26	0.88
1 to 3.....	66	1.019	0.61	0.40	0.94	0.62
3 to 5.....	160	1.016	0.39	0.62	0.85	1.36
5 to 7.....	300	1.009	0.27	0.74	0.29	0.87
7 to 9.....	775	1.007	0.19	0.90	0.30	1.43
9 to 7.....	400	1.016	0.40	1.60	1.10	4.40
Total.....	1,983	5.51	11.03

* In the observations of April 27 and 30 the tests were not very satisfactory owing to the inability of the patient to void at regular intervals and to the small amount of food she was taking. On June 8, when the blood picture had changed from hemoglobin 19 per cent. and red blood corpuscles 460,000 on April 26 to hemoglobin 74 per cent. and red blood corpuscles 2,510,000 on June 3, following treatment, the observations on renal function showed a marked return toward normality.

A glance at the tables and illustrations shows a very evident tendency to fixation in the curve of the specific gravity. Similarly there is fixation in the percentage concentration of the sodium chlorid, with a much less tendency toward fixation in the percentage concentration of the nitrogen. A number of the patients also show a tendency toward an increased amount of night urine, such as is found in cases of chronic nephritis.

In only one patient with pernicious anemia have we failed to find this type of renal function described above. This was a patient who when studied had relatively little anemia, though the blood showed the morphology typical of pernicious anemia. Her excretion (Fig. 4) of water, sodium chlorid and nitrogen showed no fixation in the forenoon, but in the afternoon there was a tendency to fixation at high levels. This type of excretion we have learned to associate with the very early stages of chronic nephritis, an early hypersensitivity of the kidney, followed by evidence of fatigue in the afternoon. Interestingly enough this particular patient had hypertension and other evidence of early chronic nephritis. The details of the blood picture, renal tests, etc., of this patient follow.

CASE 14 (P. B. B. H., Med. No. 4430).—A woman, aged 60, was given a blood examination March 31, which showed hemoglobin 78 per cent., red blood corpuscles 2,320,000; and on April 2, hemoglobin 84 per cent., red blood corpuscles 2,510,000. The phenolsulphonephthalein excretion on April 3 was 49 per cent. in two hours.

The urine on March 31 showed the slightest possible trace of albumin and a moderate number of hyaline and finely granular casts; the same condition existed on April 2.

The treatment was Fowler's solution from April 2 to April 6.

TABLE 21.—TWO-HOUR RENAL TEST IN CASE 14, MADE APRIL 5, 1916

Time	Volume, C.c.	Specific Gravity	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
7 to 9.....	40	1.026	0.61	0.24	0.62	0.25
9 to 11.....	620	1.003	0.09	0.36	0.12	0.74
11 to 1.....	195	1.009	0.17	0.33	0.28	0.55
1 to 3.....	43	1.024	6.66	0.28	0.58	0.25
3 to 5.....	160	1.018	0.34	0.54	0.88	1.41
5 to 7.....	85	1.022	0.54	0.47	0.91	0.80
7 to 9.....	125	1.022	0.66	0.83	0.88	1.10
9 to 7.....	330	1.018	0.44	1.45	0.81	2.67
Total.....	1,601	4.70	7.77

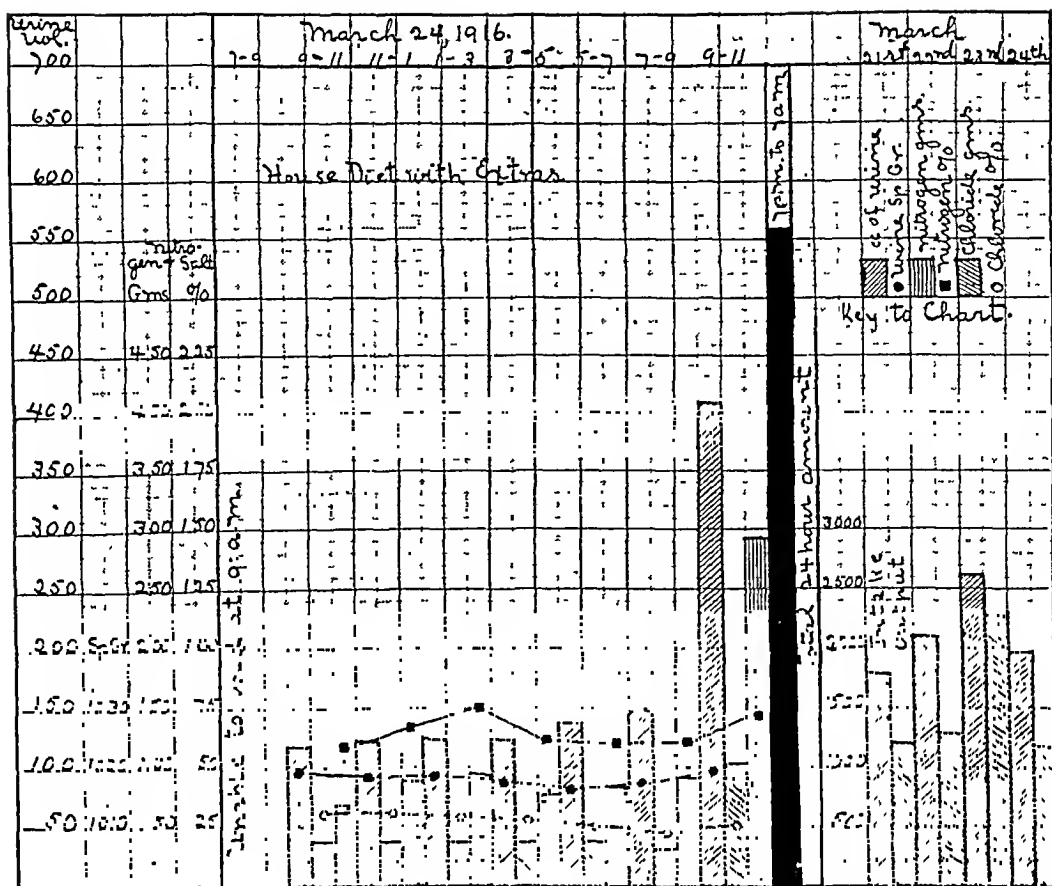


Fig. 3 (Case 1, P. B. B. H., Med. No. 4318).—Diagnosis, pernicious anemia. This figure shows graphically the fixation in the curves of excretion, similar to the condition in Figure 2, from a patient with severe chronic nephritis. (For the key to this figure see Figure 1.)

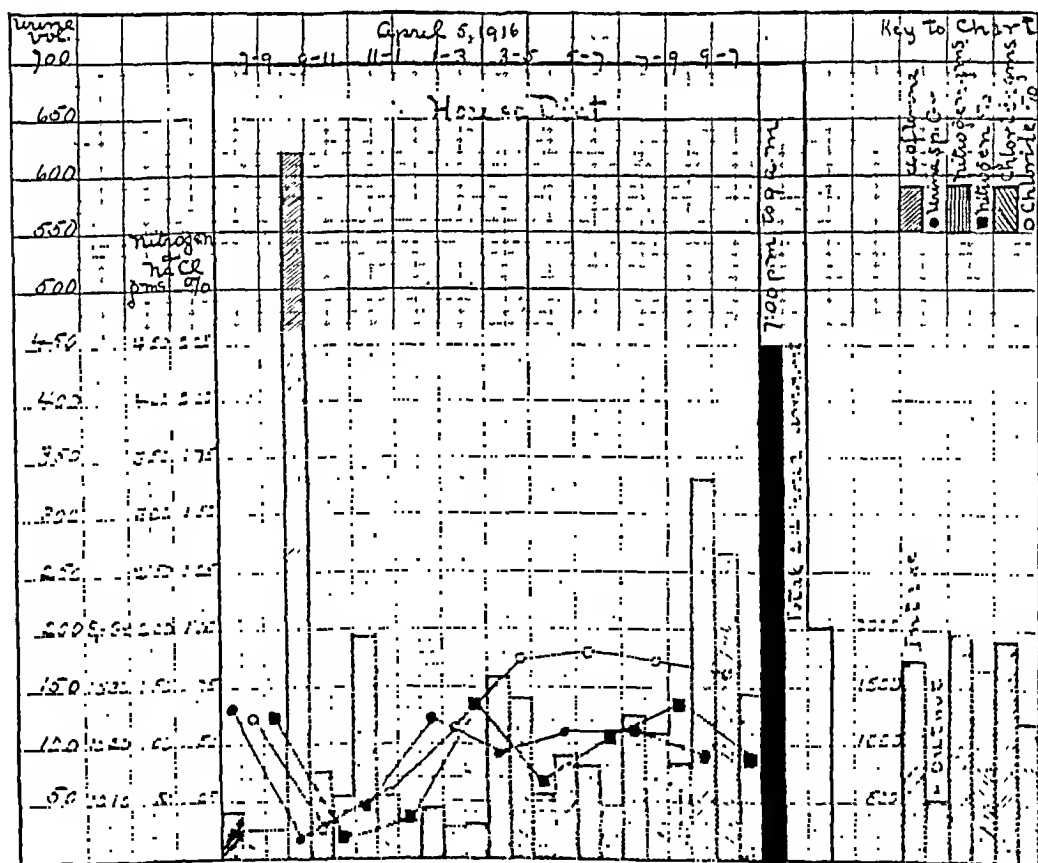


Fig. 4 (Case 14, P. B. B. H., Med. No. 4430).—Diagnosis, pernicious anemia, with very slight anemia and an early stage of chronic nephritis. The illustration shows graphically the lack of fixation in the curves of excretion. The similarity of the curves in Figure 1 from a patient without renal disturbance is quite evident. (For the key to this figure see Figure 1.)

COMMENT

The data given indicates that in a severe anemia renal function, as measured by dietary tests, is disturbed in much the same way as is found in patients with advanced chronic nephritis. In the patients which we have studied are included both young and old. In the latter the element of arteriosclerosis and moderate organic renal lesions of nephritic nature can not be excluded, but in none of these patients except the one in Case 14 was there any evidence in the way of symptoms or physical findings of a renal lesion of the nature of chronic nephritis, and in the younger patients at least the probability of such without symptoms of nephritis is very slight. It seems more probable that this disturbance in excretion is the result of the anemia, either a nutritional or a toxic disturbance in renal cellular activity. This view is supported by the improvement in renal function with improvement in blood condition and by the absence of fixation in Case 14, in which anemia was very slight and the excretion picture very different from the other cases.

Inasmuch as in pernicious anemia the dietary renal test gives a picture similar to that in quite advanced nephritis, caution is required in the interpretation of the results of these tests in patients supposed to have nephritis. If a patient with moderate nephritis, as indicated by other tests and by symptoms, happened to have a fairly severe anemia, this latter factor might give to the picture of renal excretion a fixation suggestive of advanced nephritis and lead to a prognostic interpretation which was unjustifiably poor. Consequently, it will be well to consider the element of anemia when drawing conclusions from dietary renal tests applied to patients with nephritis, though it is not probable that this will prove a complicating factor in many cases, for usually the degree of anemia in patients with nephritis is slight, much less than their pallor would suggest.

CONCLUSIONS

In patients with pernicious anemia the disease is accompanied by a disturbance of renal function, as measured by renal dietary tests, which is similar to that found in patients with advanced chronic nephritis. In these patients there is no other evidence of chronic nephritis and the disturbance appears to be due to the anemia, decreasing with the subsidence of the severity of the anemia unless the anemia is maintained so long that a permanent disturbance of renal function ensues.

My thanks are due to Miss Russell and Miss Cate, chemical technicians in the hospital laboratory, for the quantifications made in this series of cases.

AUTOGENOUS DEFIBRINATED BLOOD IN THE TREATMENT OF BRONCHIAL ASTHMA *

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INTRODUCTION

The correct interpretation of results in the treatment of bronchial asthma presents an exceedingly difficult problem. So chronic, so distressing, so intractable is this malady that any new procedure which appeals to the sufferer and carries with it the slightest hope of relief may produce at least a temporary amelioration of the symptoms. We must be careful, therefore, not to fall into the error of overestimating the value of any new treatment. It is only by repeated observations over a long period of time that any conclusive interpretation can be made. However, six successive cases of bronchial asthma responded so favorably, in our opinion, to the repeated subcutaneous injections of autogenous defibrinated blood as to warrant at least a preliminary report of the cases, the treatment and the theoretical considerations that prompted us to employ this method of therapy and that may help to explain the results obtained.

PURPOSE AND SCOPE OF THE WORK

The work reported in this paper was undertaken with certain definite limitations. Only patients with so-called essential bronchial asthma were treated, not those suffering from dyspnea of renal, cardiac or mediastinal origin. Moreover, we eliminated from our work all patients with bronchial asthma in whom a peripheral causal factor like the nasopharynx could be found. No attempt has been made in this paper to summarize the historical data, the innumerable methods of treatment of asthma or the various theories as to its nature and pathogenesis. Our aim is simply to give the results of a method of treatment undertaken in the course of clinical and experimental research in asthma and explained, we believe, on a rational hypothesis.

TECHNIC

Autoserotherapy has been used in effusions into the various serous cavities of the body, in psoriasis and other skin diseases, and in a number of other conditions. In many cases the employment of this method was empirical; in other cases the treatment was not sufficiently intensive to warrant conclusive results. The method we adopted differed from that of other authors.

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In each of our cases phlebotomy was performed by venepuncture, with a sterile needle. From 20 to 30 c.c. of blood were withdrawn and received in a sterile one-ounce flask containing a number of glass beads. The contents were agitated for from five to seven minutes to separate the fibrin. The defibrinated blood was then drawn into a 30 c.c. syringe and immediately injected subcutaneously into the loin of the patient. Ten injections at intervals of about one week were made in each case. Whenever possible blood was withdrawn during an asthmatic attack, but for obvious reasons this was not always feasible. There were no local or immediate general effects following the injections.

REPORT OF CASES

Brief abstracts of the cases and their treatment follow. Only those patients who received ten injections are here reported. The results of the treatment in other cases now still under observation we expect to report in a future publication.

CASE 1.—P. B., a Russian, aged 55, gave a negative family and past history except that he had snuffed tobacco for many years.

His present illness began nine months before, after exposure to rainy and chilly weather. He was suddenly seized with an attack of shortness of breath lasting several hours, during which there was wheezing in his chest, followed by expectoration and relief. Similar attacks occurred with increasing severity and frequency. At times the patient had to sit up in bed at night until an attack would abate. He had had no hemoptysis or other symptoms except for a sensation of oppression in the epigastrium.

The physical examination revealed a well-built man with an asthmatic type of chest. The lungs showed signs of emphysema. The weight was 154 pounds. The auscultatory systolic blood pressure was 140 mm. of mercury and the diastolic pressure was 85 mm. (Tyco's). The urine was normal and the Wassermann test was negative.

Treatment at first consisted of intravenous injections of the patient's serum in amounts of 5 to 8 c.c. at weekly intervals. A phlebotomy was done, the blood received in a sterile vessel and kept in the refrigerator an average of eighteen hours. The serum was then injected. In later injections the serum was separated by immediate centrifugalization and given intravenously. Finally, however, we thought it best to use defibrinated blood, and make the injections subcutaneously, a procedure which we carried out in all the subsequent cases. The amounts reinjected varied from 15 to 25 c.c.

The first injection was given May 24, 1915. After the first few injections, the patient felt improved. He progressively gained in weight, reaching 160 pounds in July and 170 early in September. In the latter month, however, he had a mild attack and requested further treatment. Three more injections of 25 c.c. each of defibrinated blood were given at weekly intervals. His physician, who referred the case, informs us that he had no further attacks.

CASE 2.—F. G., a Russian, widow, aged 32, gave a negative family history and had had no diseases or operations.

Four years before, the patient began to suffer from attacks of bronchial asthma, which had continued to the time of the beginning of treatment. The attacks recurred at intervals of a few days up to six weeks, and lasted from one to three days. During the attacks she had marked dyspnea, inability to cough or even speak, profuse perspiration and finally exhaustion. At the end of the

attacks the cough became more productive. She had never had hemoptysis, but had lost much weight.

The physical examination showed a woman of small build with the characteristic asthmatic type of chest. The heart was normal. The lungs showed scattered crepitations, but no wheezing râles at the time of the first examination. The auscultatory systolic blood pressure was 115 mm. of mercury, and the diastolic was 75 mm. (Tycos). The Wassermann test was negative. The urine was normal and the sputum, examined perhaps thirty times, showed no tubercle bacilli.

Ten subcutaneous injections of the patient's defibrinated blood were given at intervals of about one week, the amounts varying from 15 to 25 c.c. During the week after the first injection the patient felt better and stated that her previous intervals of relief had never been so complete. But the day after the second injection she had sneezing and cough which developed into an attack of considerable severity. The patient stated that no previous attacks were preceded by nasal symptoms or cough. The lungs showed prolonged expiration and scattered wheezing râles. The patient had a few more mild attacks, but after three injections they ceased and she began to gain in weight. The first injection was given Oct. 2, 1915, when she weighed 89 pounds. At the end of the treatment she weighed 92. Since then the patient has had no attacks of asthma, has gained about 9 pounds in three months, and but for a slight morning cough, states that she has felt remarkably well despite sudden changes of temperature and weather. Formerly she was unable to walk two blocks on account of dyspnea. She has lately been walking ten to fifteen blocks without any trouble twice daily, and has been working steadily.

CASE 3.—A. O., a Russian, aged 35 years, gave a negative family history, and had previously been in excellent health except for occasional attacks of bronchitis. Three and a half years previously some nasal operation was performed. Two years before an appendectomy was done, since which time the present illness dates.

For two years the patient had suffered from spasmodic attacks of shortness of breath, wheezing in the chest, worse on exertion, moderate cough and expectoration, associated with a sensation of oppression in the epigastrium and lower half of the chest. These attacks occurred very frequently, averaging about four or five a week. The patient felt better indoors, but was not affected by walking in fields or woods.

Physical examination revealed a man weighing 218 pounds, with an emphysematous chest with an expansion of only 2.5 cm. between complete expiration and deep inspiration. The auscultatory systolic blood pressure was 140 mm. of mercury and the diastolic pressure was 90. The urine was normal and the Wassermann test was negative.

During the earlier period of his treatment we occasionally witnessed a typical paroxysm during which he was dyspneic and cyanotic, with his chest filled with wheezing and musical râles.

At intervals of about one week the patient received ten subcutaneous injections of defibrinated blood, according to the method above described. The amount varied from 15 to 22 c.c. The first injection was made Sept. 27, 1915, and the last on Dec. 12, 1915. After the first three injections the patient felt unimproved. He still had attacks of dyspnea and cough, with profuse expectoration and wheezing in his chest. Then the attacks ceased and have not reappeared since. In their stead he had for several weeks an almost constant cough with expectoration and fits of sneezing, soon succeeded by a severe frontal headache, which has somewhat lessened since.

At the time of the last injection and after that the patient stated that he felt much improved, in fact, that he had not felt so well at any time since the onset of his asthma. At one time he had a severe coughing spell which he feared might precede an attack, but none ensued. He has had no attacks in the past eighteen weeks following the termination of treatment.

His lungs at first showed, almost constantly, abundant wheezing râles. These have disappeared, though the expiration is still prolonged on account of the emphysema.

CASE 4.—G. F., a Hungarian, aged 30, gave a negative family and past history except for a hemorrhoid operation five years before.

The present illness dates back five years, when he commenced to have frequent colds and then typical attacks of bronchial asthma. He had dyspnea and a sense of oppression in the chest with cough and slight expectoration. A nasal operation performed two years before proved of no benefit. His attacks occurred weekly, but more often in winter. They were always aggravated by inclement weather, and seemed to bear no relation to the patient's diet.

Physical examination showed a typical asthmatic condition of the chest with diffuse wheezing and sonorous râles. The chest expansion was only 2 cm. The urine was normal. The Wassermann test was negative.

Treatment consisted of weekly subcutaneous injections of the patient's defibrinated blood, 15 to 25 c.c. each time, beginning Sept. 17, 1915.

For the first six weeks the patient stated that he felt practically well and had no attacks. He then had one mild attack and none after that until Feb. 8, 1916, when he had one severe attack. The patient stated, however, that for one year prior to the injections the attacks were almost constant. After the cessation of treatment the attacks were very mild and infrequent. The lungs still showed slight wheezing and prolonged expiration eight weeks after treatment was stopped.

CASE 5.—J. K., a Russian woman, aged 29, had a negative family and past history.

The present illness dates back many years (from the time she was three days old, she was told). She had attacks of dyspnea and wheezing in the chest of sudden onset, occurring about twice a week. There was sometimes an interval of a month between attacks, but rarely any longer.

The physical examination showed a congested throat and a slightly enlarged thyroid. The lungs showed a few piping basic râles. The chest expansion showed a variation of 4 cm. between deep expiration and deep inspiration. The urine was negative. The Wassermann test was negative.

The treatment consisted of subcutaneous injections of the patient's defibrinated blood at weekly intervals. About 15 c.c. were given each time. During the course of the treatment the patient had only two very mild attacks which occurred with severe changes of weather, and gained seventeen pounds in weight. Her lungs were clear with slightly prolonged expiration.

During the eight weeks following the last injection the patient had no attacks of asthma.

CASE 6.—P. F., a Russian woman, aged 29, gave a family history of asthma. In her past history there had been no illnesses or operations.

Four years previously, the patient began to cough, with profuse mucous expectoration. Then she was seized with attacks of dyspnea, which came rapidly and unannounced, with a sensation of oppression in the epigastrium and the front of the chest. She frequently had to sit at an open window and gasp for breath. Such attacks were repeated almost every night. During the five pregnancies which the patient went through she stated that she had practically no paroxysms. In the intervals between attacks she had only slight cough and substernal oppression. She would occasionally sneeze spasmodically eight to ten times during the day, and found that when the nasal symptoms predominated, the chest condition improved.

The physical examination revealed an emphysematous chest with slight wheezing over both lungs. The weight was 181 pounds. The urine was normal, and the Wassermann test was negative.

The treatment consisted of subcutaneous injections of the patient's defibrinated blood at intervals of about one week, the amounts given being 20 to 25 c.c. each time. The first injection was given Oct. 15, 1915.

Though after several injections the patient still had attacks, they were mild and infrequent while before the injections they were an occurrence of almost every night. In four months she had gained 2 pounds and stated that she felt the injections had helped greatly, and that during the treatment she was as well as four years before, when her condition was only incipient. After that she had a few mild attacks. Her weight at the termination of treatment was 189 pounds, a gain of eight pounds. The auscultatory systolic blood pressure was 115 mm. of mercury, and the diastolic pressure was 75 mm. (Tycos).

She became pregnant two months after the end of the treatment, and as she stated that pregnancy seemed a preventive of attacks of asthma in her case, the future course of her condition, if improved, may be attributed to that as much as to the treatment.

THEORETICAL CONSIDERATIONS

The process of reasoning by which we concluded that autogenous defibrinated blood might be of benefit in bronchial asthma may be summarized in the following outline, each step of which will be discussed later in detail:

1. Asthma is due to a spasm of the smaller bronchi.
2. Spasm of the bronchi in asthma is a manifestation of anaphylaxis.
3. The anaphylactic phenomena may be explained on the basis of protein sensitization.
4. Whether the protein gains access to the body by the nasopharynx, by the gastro-intestinal tract, by the respiratory system or by some other portal, it is probably absorbed by the blood; if so, it should be found in the blood, especially just prior to or during an asthmatic attack.
5. The rational method of active immunization in anaphylaxis consists of repeated injections of small doses of the causal protein; if the previous premises are true in asthma, immunization by repeated parenteral injections of autogenous defibrinated blood, obtained preferably during a paroxysm, should be beneficial.

ASTHMA A RESULT OF SPASM OF THE BRONCHIOLES

That the attacks of asthma are the result of muscular spasm of the smaller bronchi was originally stated by Reisseisen¹ and has been most ably contended by Hyde Salter² as far back as 1858. The excellent work of Beer,³ Riegel,⁴ Lazarus⁵ and others has gone far to confirm this hypothesis. The experiments of Brodie and Dixon⁶ have clearly

-
1. Reisseisen: *System of Medicine*, Allbutt and Rolleston, London, 1909, v, 51.
 2. Salter: *On Asthma, Its Pathology and Treatment*, New York, 1882.
 3. Beer: *Arch. f. Anat. u. Physiol.*, 1892, Supplement, p. 101.
 4. Riegel and Edinger: *Ztschr. f. klin. Med.*, 1882, v, 413.
 5. Lazarus: *Deutsch. med. Wchnschr.*, 1891, xvii, 852.
 6. Brodie and Dixon: *Tr. Path. Soc. London*, 1903, liv, 17; *Jour. Physiol.*, 1903, xxix, 97.

demonstrated the typical relationship between bronchial spasm and the syndrome known as bronchial asthma. Stimulation of the constrictor fibers of the vagus by muscarin or pilocarpin or by electricity invariably results in the production of the signs and symptoms of bronchial asthma. Further evidence favoring this theory is afforded by the sudden onset and almost equally as sudden a cessation of the asthmatic attack—the usual occurrence in spasm of any involuntary muscle.

The hypothesis next in order of importance is that which assumes a rapid turgescence of the mucous membrane of the bronchioles. This seems to be less tenable and is being discarded by many. The various other theories as to the causation of bronchial asthma need not be discussed in this paper.

ASTHMA AND ANAPHYLAXIS

Studies in anaphylaxis have of late years served to make clearer the conception of the pathogenesis of asthma. Richet and Hericourt in 1898 applied the name anaphylaxis to the syndrome which results from the injection of a soluble protein into an animal sensitized to it.⁷ This syndrome consists of marked respiratory distress, analogous to an asthmatic paroxysm, cyanosis, vomiting, and asphyxia, which may prove fatal.

The work of Meltzer⁸ and the experimental studies of Auer and Lewis tend to prove that the asthmatic individual is sensitized to a definite substance, and that an asthmatic attack sets in every time this substance happens in some way to enter into the circulation of the individual. In the actual processes which take place in nature the effective doses may be infinitely small. It may well be possible that the minute quantities contained in the emanation from horses, cats or guinea-pigs are sufficient to act as a toxic dose, and to call forth the nonfatal stenosis of the bronchi evidently present in an asthmatic attack. Auer and Lewis' investigations seem definitely to establish acute anaphylactic death as being caused by respiratory failure consequent on stenosis of the bronchi.⁹ The resulting asphyxia is due to an inspiratory immobilization of the lungs.

Gillette collected, up to 1909, fifteen fatal cases and thirteen non-fatal cases of severe anaphylaxis following injections of horse serum.¹⁰ Of the total twenty-eight cases, eighteen were in asthmatics, of whom nine died. Inasmuch as these reactions were due to horse serum, it is noteworthy that in a number of these individuals previous asthmatic attacks were incited by being near horses.

7. Richet: *Compt. rend. Soc. de biol.*, 1898, v, 137.

8. Meltzer: *Jour. Am. Med. Assn.*, 1910, iv, 1022.

9. Auer and Lewis: *Jour. Am. Med. Assn.*, 1909, liii, 458.

10. Gillette: *Therap. Gaz.*, 1909, xxxiii, 159.

ANAPHYLAXIS AND PROTEIN SENSITIZATION

When a foreign protein gains entrance into the body, it has been shown that certain cells develop a specific digestive ferment which splits up the invading protein. The resulting split products, according to Vaughan,¹¹ possess the property of sensitizing the individual to the unbroken molecule. The first or sensitizing dose of protein injected into an animal is digested, but the process goes on so slowly that no toxic effect is evident. An immediate effect on reinjection depends on the rapidity with which the protein is split up and its poisonous constituent set free.

Certain digestion products of the proteins may now and then become absorbed in an abnormal stage into the circulation from the alimentary canal and produce an asthmatic attack. Babcock considers asthma an anaphylaxis due to the absorption of bacterial protein from some focus of infection.¹² He believes the focus is most frequently located in the respiratory tract itself, but may be in the gallbladder or in other parts of the body.

Though poisonous molecules may be bacterial, vegetable or animal in origin, they are not distinguishable in physiologic effect, all having the property of exciting the anaphylactic attack.

THE PROTEIN IN THE CIRCULATION

If we assume then that asthma is an anaphylactic reaction due to the introduction into the system of a foreign protein, the next step is to attempt to identify this protein, or if that is not possible, to discover its source, portal of entry and localization. Comparatively little work has been done along this line. We are now attempting some researches in this connection which may prove of some value and which will be reported in a future publication.

In its analogous malady, hay-fever, Koessler attempted to demonstrate the presence of pollen protein free in the circulating blood of patients suffering with a seasonal attack.¹³ He took blood from a patient during an attack of hay asthma. Five c.c. of serum were injected subcutaneously into each of four guinea-pigs. Twelve to eighteen days later an intracardial injection was made of 1 to 10,000 dilution of an extract of ragweed pollen, and three out of the four guinea-pigs showed symptoms of anaphylaxis. The deduction that Koessler made from his experiment was that there was a pollen protein in the serum of his patients. Friedberger¹⁴ has shown that the serum

11. Vaughan: *Am. Jour. Med. Sc.*, 1913, cxlv, 161; *Protein Split Products*, New York, 1913.

12. Babcock: *Jour. Am. Med. Assn.*, 1915, lxxv, 1942.

13. Koessler: *Illinois Med. Jour.*, 1914, xxvi, 120.

14. Friedberger: *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, 1910, iv, 636.

of rabbits treated with a large dose of sheep serum is capable by itself, when injected intravenously, of producing anaphylactic shock in guinea-pigs sensitized to sheep serum. From this he argues that a small amount of sheep serum remained uneliminated from the rabbits' circulation.

Weil has shown that the biologic reaction between antigen and antibody takes place in the cells of the body, such as involuntary muscle, and not in the circulating blood;¹⁵ the assumption is that the antigen reaches the cells through the circulation and may there, in transit, be discovered.

Similarly Schloss¹⁶ believes that the occurrence of an urticarial lesion from cutaneous inoculation of toxic foods is directly comparable to the more striking clinical effects produced by their ingestion, inasmuch as they must in the latter case necessarily reach the skin through the circulation.

The assumption seems therefore warranted that just prior to the occurrence of an anaphylactic attack, and clinically at the time of onset and probably also during an attack of asthma, the toxic protein which excites the attack is free in the circulating blood.

IMMUNIZATION IN ANAPHYLAXIS AND ASTHMA

Active immunization to the toxic protein in anaphylaxis may be obtained by injecting the protein in small amounts subcutaneously in successive doses at short enough intervals and over a long enough period of time. Schloss succeeded in immunizing five cases of egg-sensitization by feeding small doses of egg-albumin. In one case of urticaria, treatment was begun by the administration of 2 mg. of ovomucoid in capsules three times daily. The dose was increased at first gradually and then more rapidly. The progress of immunization was determined by means of the cutaneous reaction. The latter finally became negative and the patient was completely immunized to egg or ovomucoid.

Goodale has recorded the case of a patient with horse asthma with a high initial sensitization to horse serum, who acquired an evident increase in resistance in the course of thirty parenteral injections of progressively increasing doses of horse serum.¹⁷ He determined the increase in resistance by the application of horse serum to an abrasion of the skin, which in sensitized individuals produces a sharply localized edema and reddening within a few minutes. Levison¹⁸ treated two

15. Weil: *Jour. Med. Research*, 1914, xxx, 87; *ibid.*, 1915, xxxii, 107.

16. Schloss: *Am. Jour. Dis. Child.*, 1912, iii, 341.

17. Goodale: *Boston Med. and Surg. Jour.*, 1915, clxxii, 751; *ibid.*, 1915, clxxiii, 42.

18. Levison: *New York Med. Jour.*, 1915, cii, 901.

patients with horse asthma in the same way with similar beneficial results.

Babcock, assuming the existence of an infectious focus in the body from which the foreign protein is absorbed, considers autogenous vaccines the logical procedure in the treatment of asthma. In 1913 Duncan¹⁹ attempted to immunize a patient suffering with asthma by repeated injections of filtered toxins from the patient's sputum.

Rosenau and Amoss²⁰ asserted that the condensed expired air from human beings contains a substance which sensitizes guinea-pigs to human blood serum. One of us (Kahn),²¹ in collaboration with Weisman, made observations on the effect on asthma of the injection of liquid from human expired air. The injection was made into the median basilic vein of two persons, one who was normal receiving 5 c.c., and another, aged 30, who had been a sufferer with bronchial asthma, receiving 8 c.c., during an interval between attacks. There were no immediate or after effects noted in either case. The further work of Weisman definitely disproved the statements of Rosenau and Amoss that the breath contains a "volatile" protein, and that such "volatile" protein is an important respiratory factor.

Holbrook Curtis,²² Dunbar,²³ Noon and Freeman,²⁴ Clowes²⁵ and Koessler have used the method of active immunization in hay-fever. More recently Oppenheimer and Gottlieb²⁶ have reported favorably on the injection of very small amounts of pollen extract at about weekly intervals just previous to or during a seasonal attack. They used the cutaneous test to discover the specific causal pollens. Hays²⁷ reported twelve patients with hay-fever most of whom received two subcutaneous injections of from 5 to 10 c.c. of autogenous serum. He reported negative results.

COMMENT

In bronchial asthma there seems to exist a theoretical foundation for this method of treatment. With each attack of asthma there occurs a sudden or gradual liberation into the circulating blood of the protein which excites the attack. If then, during that period blood is withdrawn, it presumably contains the toxic protein or antigen. This can now be considered equivalent to the isolation of the substance which is to be used for active immunization, regardless of its source of origin. Repeated injections of this defibrinated blood subcutaneously are made

19. Duncan: *New York Med. Jour.*, 1913, xcvi, 1278.

20. Rosenau and Amoss: *Jour. Exper. Med.*, 1913, xvii, 132.

21. Weisman: *Biochemical Studies of Expired Air in Relation to Ventilation*, Diss., Columbia Univ., New York, 1913.

22. Curtis: *New York Med. News*, 1900, lxxvii, 16.

23. Dunbar: *Deutsch. med. Wchnschr.*, 1911, xxxvii, 578.

24. Noon and Freeman: *Lancet*, London, 1911, i, 1572.

25. Clowes: *Soc. for Exp. Biol. and Med.*, 1913, x, 48.

26. Oppenheimer and Gottlieb: *New York Med. Jour.*, 1915, ci, 229.

27. Hays: *Ann. Otol., Rhin. and Laryng.*, 1915, xxiv, 285.

at varying intervals. The quantities of antigen contained in each injection are so minute as to create a very small amount of antibody each time, and never to result in an attack. Thus the tolerance of the body for the protein may be enhanced.

Naturally in an ideal course of treatment it would be desirable to obtain the blood each time just prior to or early during an attack of asthma, since we assume that it is then that the antigen is in the circulation in the greatest amount.

It is possible that the benefit from the treatment may rest on an empirical basis. The objection may be raised that the amount of antigen in circulation is greater than we can withdraw for reinjection. Especially can it be contended that the mere withdrawal of blood from the circulation and its reintroduction subcutaneously is not sufficient to produce a marked biologic effect on the involuntary muscles. It may also be said that the original presence of antigen in the circulation should itself serve to immunize the individual. But this, we know, does not take place in asthma, whereas the clinical results from the treatment would seem to permit of our foregoing interpretation.

It is obvious that the cases reported are too few from which to draw any definite conclusions as to the efficiency of autotherapy with defibrinated blood. But the results in these cases are promising enough to justify a continuation of the treatment and to find in what proportion of the cases it is of benefit, and to what degree.

In a disease in which the physical signs are so transitory as they are during the attacks of bronchial asthma, improvement or amelioration should not be judged merely by the changes in physical signs. The patient's subjective sensations should bear at least equal if not greater weight in forming our opinion of betterment.

CONCLUSIONS

1. Inasmuch as bronchial asthma is due, in our opinion, to sensitization by a foreign protein, immunization by injection of the causal protein should be of benefit.

2. Autogenous defibrinated blood, obtained preferably during the attacks of asthma, we assume may serve as antigen for treatment by active immunization.

3. Six successive patients with bronchial asthma, treated by repeated injections of autogenous defibrinated blood, have shown definite improvement as indicated by diminution in frequency and severity of attacks, gain in weight, increased ability to work and improved subjective symptoms.

We wish to thank Dr. Isidor N. Kahn and Dr. N. Breiter for their kind interest in this work and for referring several of the cases to us for treatment.

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THE ALBUMIN AND GLOBULIN CONTENT OF HUMAN BLOOD SERUM

IN HEALTH, SYPHILIS, PNEUMONIA, AND CERTAIN OTHER INFECTIONS,
WITH THE BEARING OF GLOBULIN ON THE WASSERMANN
REACTION *

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In spite of numerous results found in literature, the albumin and globulin content of serum in health and disease has been reinvestigated by use of Robertson's¹ method, because of the simplicity and freedom from possible error of the new technic as compared with that of former methods. The small amount of serum used is another advantage and has made possible the use of two controls on each serum examined by the writer. The results which can be obtained are uniform, especially if the writer's suggestions about the technic, which will soon be published, are followed and his automatic pipet² is used to assure accuracy of measurements.

During the last seven months a number of normal serums have been examined. The average results differ slightly from those obtained by Robertson's method previously reported.³ The total protein is lower than in the previous series, due to the fact that serums were taken, except in a few cases, from patients who were confined to bed as a result of a fracture or uncomplicated herniotomy, or from those who had been lying down for twenty-five or more minutes. The non-proteins are slightly higher, while the percentage of globulin in the total protein is moderately increased. The last four serums were taken from the same person at different times throughout a period of six months. The values are quite uniform (Table 3).

LITERATURE

The literature contains many results for the normal value of serum proteins, most of which will be found in Table 1. Several of the average values were taken directly from the articles by Erben.⁴ Com-

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* From the Medical Service and Chemical Laboratory of the Massachusetts General Hospital.

1. Robertson, T. B.: *Jour. Biol. Chem.*, 1915, xxii, 233.

2. Rowe, A. H.: *Jour. Lab. and Clin. Med.*, 1916, i, 439.

3. Tranter and Rowe: *Jour. Am. Med. Assn.*, 1915, lxxv, 1433.

4. Erben, F.: *Zetschr. f. klin. Med.*, 1903, 1, 450; *ibid.*, 1900, xl, 266, 282; *Ibid.*, 1902, xlvii, 302; *Ztschr. f. Heilk.*, 1905, xxvi, 245, 303, 449.

TABLE 1.—NORMAL VALUE OF SERUM PROTEINS AS FOUND IN THE LITERATURE

Investigator	Where Found	Date	Percentage of Total Protein
Berzelius.....	Erben: Ztschr. f. klin. Med., 1903, l, 450; <i>ibid.</i> , 1900, xl, 266, 282; <i>ibid.</i> , 1912, xlvii, 302; Ztschr. f. Heilk., 1905, xxvi, 245, 303, 449	1831	8
Marett.....	Erben: Ztschr. f. klin. Med., 1903, l, 450; <i>ibid.</i> , 1900, xl, 266, 282; <i>ibid.</i> , 1912, xlvii, 302; Ztschr. f. Heilk., 1905, xxvi, 245, 303, 449	1831	8.7
Denis.....	Erben: Ztschr. f. klin. Med., 1903, l, 450; <i>ibid.</i> , 1900, xl, 266, 282; <i>ibid.</i> , 1912, xlvii, 302; Ztschr. f. Heilk., 1905, xxvi, 245, 303, 449	1838	8
Lecanu.....	Erben: Ztschr. f. klin. Med., 1903, l, 450; <i>ibid.</i> , 1900, xl, 266, 282; <i>ibid.</i> , 1912, xlvii, 302; Ztschr. f. Heilk., 1905, xxvi, 245, 303, 449	1837	7.8 to 8.1
Bostok.....	Erben: Ztschr. f. klin. Med., 1903, l, 450; <i>ibid.</i> , 1900, xl, 266, 282; <i>ibid.</i> , 1912, xlvii, 302; Ztschr. f. Heilk., 1905, xxvi, 245, 303, 449	1842	10
Nasse.....	Erben: Ztschr. f. klin. Med., 1903, l, 450; <i>ibid.</i> , 1900, xl, 266, 282; <i>ibid.</i> , 1912, xlvii, 302; Ztschr. f. Heilk., 1905, xxvi, 245, 303, 449	1836	7.2 to 9
Becquerel und Rodier.....	Gaz. méd. de Paris, 1844, Nos. 47, 48, 49, 50, 51; <i>Chémie pathologique</i> , 1854; Untersuchungen über die Zusammensetzung des Blutes in gesunden und Kranken Zustände, übersetzt von Eisenmann, Arlangen, 1845	1845	5
Otto.....	Erben: Ztschr. f. klin. Med., 1903, l, 450; <i>ibid.</i> , 1900, xl, 266, 282; <i>ibid.</i> , 1912, xlvii, 302; Ztschr. f. Heilk., 1905, xxvi, 245, 303, 449	1848	7.5 to 6
C. Schmidt.....	Charakteristik der epidem. Cholera, Leipzig, 1850, p. 30; reference from Joachim	1850	7.4 to 8.3
Leven.....	Malay's Jaresberleht, 1873, l, 115.....	1873	7.9
Hammarsten.....	Arch. f. d. ges. Physiol., 1878, xvii, 413; Ergebn. d. Physiol., 1902, l, 348; Lehrbuch der physiologischen Chemie, 1914	1878	7 to 8.1
Hoffman.....	Arch. f. exper. Path., 1882, xvi, 133.....	1882	7.4 to 7.8
Limbeck and Pick.....	Prag. med. Wehnsehr., 1893, xviii, 21, 133, 149, 165; Deutsch. med. Wehnsehr., xx, 563. Limbeck; Grundriss einer klin. Path. d. Blutes, Ed. 2., Jena, S. Fischer, 1896, p. 100	1893	6.5 to 7.4
Von Jaksch.....	Ztschr. f. klin. Med., 1893, xxiii, 187.....	1893	6 to 8.9
Lewinsky.....	Arch. f. d. ges. Physiol., 1903, c, 611.....	1903	6.7 to 7.6
Erben.....	Erben: Ztschr. f. klin. Med., 1903, l, 450; <i>ibid.</i> , 1900, xl, 266, 282; <i>ibid.</i> , 1912, xlvii, 302; Ztschr. f. Heilk., 1905, xxvi, 245, 303, 449	1905	8.5
Refractometrie determinations by Reiss and others	Ergbn. d. inn. Med. u. Kinderh., 1913, x, 531.....	1902 1912	7 to 9
Winternitz.....	Arch. f. Dermat. u. Syph., 1908, xciii, 65; <i>ibid.</i> , 1910, ci, 227	1908	8.2 to 8.7
Epstein.....	Jour. Exper. Med., 1912, xvi, 719; <i>ibid.</i> , 1913, xvii, 444; <i>ibid.</i> , 1914, xx, 334	1912 1913	6.4 to 8.3
Tranter and Rowe.....	Jour. Am. Med. Assn., 1915, lxxv, 1433.....	1915	6.7 to 8.7
Rowe.....	This article	1916	6.5 to 8.2

ment on these values from the literature will be found in the last portion of this review of the literature.

The best reviews of the literature on serum proteins in health and disease occur in the articles by Limbeck and Pick,⁵ Joachim,⁶ Von Jaksch,⁷ Langstein and Mayer,⁸ Erben,⁴ and Winternitz.⁹ Morawitz¹⁰ discusses the methods for determining albumin and globulin and the results obtained up to 1908 in human serum, concluding that little of importance to pathology and physiology has come from the extensive work in this field. This opinion is due, probably, to the disparity of many of the former results.

The monograph of Becquerel and Rodier¹¹ is remarkable considering the early date of its production. It covers the chemistry of the blood in health and disease in a very thorough manner. In chlorosis and plethora it was interesting to note that the total proteins were normal, while in nephritis and cardiac disease with edema, endocarditis, typhoid, acute rheumatic fever, pneumonia, secondary anemias and pulmonary tuberculosis they were decreased.

C. Schmidt¹² found serum proteins increased in severe cholera and decreased in nephritis.

Hoppe-Seyler¹³ found the serum proteins decreased in a woman with chyluria.

Leven¹⁴ obtained 7.67 per cent. of protein in the blood serum from a patient with scorbutus.

Estelle¹⁵ determined the albumin and globulin content in the blood serum of two nephritics, in one the albumin being 5.44 per cent. and the globulin 3.06 per cent., while in the other the values were 3.6 and 1.8 per cent., respectively.

Csatary¹⁶ found increased serum globulin in nephritis.

5. Limbeck and Pick: *Prag med. Wchnschr.*, 1893, xviii, 21, 133, 149, 165; *Deutsch. med Wchnschr.*, 1894, xx, 563. Limbeck: *Grundriss einer klin. Path. d. Blutes*, Ed. 2, Jena, S. Fischer, 1896, p. 100.

6. Joachim: *Arch. f. d. ges. Physiol.*, 1893, 588; *Wien. klin. Wchnschr.*, 1902, xv, 565.

7. Von Jaksch: *Ztschr. f. klin. med.*, 1893, xxiii, 187.

8. Langstein and Mayer: *Beit. z. chem. Phys. u. Path.*, 1904, v, 69.

9. Winternitz, R.: *Arch. f. Dermat. u. Syph.*, 1908, xciii, 65; *ibid.*, 1910, ci, 227.

10. Morawitz: *Blood Proteins*, Oppenheimer's *Handbuch der Biochemie des Menschen und der Tiere*, 1909, ii, Part 2, 70.

11. Becquerel and Rodier: *Gaz. méd. de Paris*, 1844, Nos. 47, 48, 49, 50, 51; *Chémie pathologique*, 1854; *Untersuchungen über die Zusammensetzung des Blutes in gesunden und kranken Zustände*, übersetzt von Eisenmann, Erlangen, 1845.

12. Schmidt, C.: *Charakteristik der epidem. Cholera*, Leipzig, 1850, p. 30, reference from Joachim.

13. Hoppe-Seyler: *Ztschr. f. physiol. Chem.*, xv, 179.

14. Leven, M.: *Maly's Jahresbericht*. 1873, i, 115.

15. Estelle: *Revue mens. de méd. et de chir.*, 1880, iv, 704.

16. Csatary: *Arch. f. klin. Med.*, 1891, xlviii, 358.

Nya-Viglezio¹⁷ found increased globulin in pneumonia, angina pectoris, tetanus, nephritis, diabetes, the values varying from 4.8 to 3.6 per cent. for albumin and from 3.5 to 3 per cent for globulin.

Von Jaksch,⁷ using serum obtained by cupping, showed a dilution of blood in acute illnesses and diseases of the heart, lungs, and kidneys. In leukemia he found 7.6 per cent protein, in pernicious anemia 7.4 per cent., in chlorosis 8.25 per cent., while in secondary anemias the protein was slightly reduced.

TABLE 2.—NORMAL VALUES FROM LITERATURE FOR ALBUMIN AND GLOBULIN WITH THE PERCENTAGE OF GLOBULIN IN THE TOTAL PROTEIN

Investigator	Where Found	Comment	Albu- min	Glob- ulin	Percent- age of Globulin
Ammansteden..	Arch. f. d. ges. Physiol., 1878, xvii, 413; Ergebn. d. Physiol., 1902, i, 348; Lehrbuch der physiologischen Chemie, 1914	Average values of 4 sera obtained by cupping*	4.34	3.22	43
Stein.....	Jour. pharm. Chemie, 1899, x, 249.....	4.89 4.63	2.86 2.77	37 37
Nya-Viglezio...	Archivio italiano di clinica medica, 1888, xxvii; reference from Joachim; Revista Clinica, 1887, xxvi, 673	5.72	2.43	30
Limbeck and Pick	Prag. med. Wehnsehr., 1893, xviii, 21, 133, 149, 165; Deutsch. med. Wehnsehr., 1891, xx, 563. Limbeck: Grundriss einte klin. Path. d. Blutes, 1896, 100	Nervous diseases (six cases)	4.8	1.7	20
Lejwinski.....	Arch. f. d. ges. Physiol., 1903, c, 611.....	3.9	2.96	43
Vinternitz.....	Arch. f. Dermat. u. Syph., 1908, xciii, 65; Ibid., 1910, ci, 227	6.2	2	24
Epstein.....	Jour. Exper. Med., 1912, xvi, 719; Ibid., 1913, xvii, 444; Ibid., 1914, xx, 334	Average values of 7 cases (varicocele, orchitis, fistula, hemorrhoids)	4.4	2.7	33
Epstein.....	One normal case.....	5.09	3.07	33
Hoffmann.....	Arch. f. exper. Path., 1882, xvi, 133.....	5.04	2.72	35

* All other values obtained from venous blood serum.

Limbeck and Pick⁵ showed an increased globulin content in the serum of nineteen cases of acute infection, though the total proteins were much reduced. Five diabetics showed increased globulin, while three cases gave low globulin. In nephritis thirteen cases showed a low total protein. The results of these writers were undoubtedly too low and were criticized by Bleibtreu.¹⁸ The latter was at fault, though, in using as his normal values those obtained from blood taken post mortem.

17. Nya-Viglezio: Archivio italiano di clinica medica, 1888, xxvii; reference from Joachim, Revista clinica, 1887, xxvi, 673.

18. Bleibtreu: Deutsch. med. Wehnsehr., 1893, xix, 1167.

E. Freund¹⁹ found that the percentage of globulin in nephritis varied from 25 to 33 per cent., while in pernicious anemia it was 33 per cent.

Emmerich and Tsuboi²⁰ stated that the globulin in blood serum decreased to zero in animals immune to hog cholera and pneumonia. This statement was never confirmed.

Seng²¹ found increased globulin in serum from animals immune to diphtheria.

Atkinson²² showed that the antitoxic power of a serum was caused by the globulins.

V. Szontagh and Wellmann²³ found that with immunization the total proteins were slightly increased.

Butjagen²⁴ confirmed the former findings of V. Szontagh.

Joachim⁵ in one article studied the protein of the blood serum, showing that globulin increased in many diseased conditions. In a second article the globulin content of ascitic fluids was determined and he also demonstrated that globulin increased at the cost of albumin when a horse was immunized to diphtheria, the albumin before immunization being 5 per cent. and afterwards dropping to 3.7 per cent.

Jakoby²⁵ found euglobulin increased in animals immunized to castor oil.

Moll²⁶ found in animals injected with various proteins, gelatin, and killed bacteria a marked increase in the globulin content and concluded that with an increase in immune bodies there goes an increase in globulin. He suggested that possibly some globulin arises from leukocytes, which suggestion first came from A. Schmidt.²⁷

Glaessner²⁸ repeated the above work, showing a moderate increase in the globulins, but not to the extent found by Moll. He could demonstrate no constant relation between the globulin and immune body formation. He suggested that the globulin has a greater resistance to the proteolytic ferment trypsin than has albumin, to account for its relative increase in disease.

Langstein and Mayer⁸ found the serum proteins increased in immunized and infected rabbits, the increase being largely in the glob-

19. Freund, E.: *Wien. klin. Rundschau*, 1895, ix, 49.

20. Emmerich and Tsuboi: *Verhandl. d. Cong. f. inn. Med.*, 1892, ii, 202.

21. Seng: *Ztschr. f. Hyg. u. Infekt.*, 1899, xxxi, 513.

22. Atkinson: *Jour. Exper. Med.*, 1900, v, 67.

23. V. Szontagh and Wellmann: *Deutsch. Med. Wchnschr.*, 1898, xxiv, 421.

24. Butjagen: *Hyg. Rundschau*, 1902, xii, 1193.

25. Jakoby: *Beitr. z. chem. Phys. u. Path.*, i, 59.

26. Moll: *Beit. z. chem. Phys. u. Path.*, 1903, iv, 563, 578.

27. Schmidt, A.: *Zur Blutlehre*, Leipzig, 1892. *Beiträger zur Blutlehre Wiesbaden*, 1895. Ref. from Hammarsten.

28. Glaessner: *Ztschr. f. exper. Path. u. Therap.*, 1905, ii, 154.

ulin fraction. They were unable to confirm the work of Emmerich and Tsuboi.

Müller²⁹ confirmed the findings of Langstein and Mayer.

TABLE 3.—ALBUMIN AND GLOBULIN CONTENT OF HUMAN BLOOD
SERUM IN NORMAL CASES

Case No.	Age	Albumin	Globulin	Total Protein	Nonprotein	Percentage Globulin
1	27*	5.85	1.97	7.82	1.2	25
2	30	5.15	2.2	7.35	1.3	30
3	36*	5	2.3	7.3	1.3	32
4	21*	5.7	2	7.7	1.3	26
5	24*	6.4	1.2	7.6	1.1	16
6	30	5	2.4	7.4	1.2	32
7	32	5.8	2.2	8	1.1	27.5
8	48	5.8	2.1	7.9	1.2	27
9	19	6	2.2	8.2	1.2	27
10	25	5.7	2	7.7	1.3	26
11	48	5.1	2.2	7.3	1.2	30
12	28	4.8	2	6.8	1.3	29
13	23	5.6	1.8	7.4	1.2	24
14	19	4.6	1.9	6.5	1.25	29
15	46	4.6	2.1	6.7	1.25	31
16	25	5.9	1.6	7.5	1.3	21
17	20	5	1.7	6.7	1.3	25
18	29	5.4	1.4	6.8	1.3	21
19	3/18/16 26	6	1.5	7.5	1.3	20
20	1/26/16* 26	6.5	1.7	8.2	1.3	21
21	10/19/16* 26	6.7	1.5	8.2	1.3	18
22	10/11/16* 26	6	1.9	7.9	1.1	24
Averages.....		5.6	1.9	7.5	1.24	25.5
Former averages.....		6.2	1.74	7.94	1.1	22

* These subjects had been walking about without doing any real work before blood was taken.

Lewinski³⁰ found the percentage of globulin a little higher in pregnant and a little lower in eclamptic women than in normal ones.

In a case of pernicious anemia Erben⁴ found 5.2 per cent. total protein, of which 4.2 per cent. was albumin and 1 per cent. globulin.

29. Müller, Paul: Beitr. z. chem. Phys. u. Path., 1905, vi, 454.

30. Lewinski; Arch. f. d. ges. Physiol., 1903, c, 611.

In parenchymatous nephritis the albumin was reduced to below 1 per cent., but was not so reduced in amyloid. The globulin was slightly increased in pericarditis. In tuberculosis the globulin was moderately increased as compared with normal values of Erben. He^e offers the suggestion of Gottwalt³¹ that the relative increase of globulin in infections is due to its greater resistance to the toxins. In a case of carcinoma a slight reduction in total protein of the serum occurred though the relation of albumin to globulin was normal. In diabetes the total protein was either slightly decreased or increased, which confirmed the findings in previous literature with the exception of those of Limbeck and Pick. In a case of chronic lead poisoning no definite changes in the serum protein occurred. In a case of typhoid no values for albumin and globulin were given.

The articles of Erben include extensive bibliographies on the entire chemistry of the blood. Normal values of all organic and inorganic substances investigated in the blood are given, together with a table of the average normal values from the literature before 1905.

Vadala,³² in two cases of anemia from ankylostomiasis, obtained the average value of 7.8 per cent. for serum albumin and 2.4 per cent. for globulin.

Grenet,³³ Gilbert and Chiray³⁴ found serum proteins decreased in liver insufficiency with and without ascites.

Winternitz⁹ found serum globulin moderately increased in syphilis.

Epstein³⁵ obtained a marked increase in globulin with a normal or very subnormal amount of total serum protein in cardiac diseases associated with decompensation and serous effusions, pulmonary and respiratory affections of inflammatory or noninflammatory origin (pneumonia, emphysema, polycythemia), diabetes mellitus and parenchymatous nephritis. Globulin was normal or decreased in achylia gastrica, tuberculosis, diabetes insipidus and chronic interstitial nephritis. In another paper he found localized infections of the kidney gave an increase in globulin, while the cases of prostatic hypertrophy and minor surgical cases gave no such increase.

The methods for determination of albumin and globulin in the past may be summarized as follows: (1) by diluting the serum ten times, precipitating out the globulin by adding salt, or obtaining the globulin by dialysis; (2) by precipitating the globulin by acetic or carbonic acid; (3) by salting out the globulin by neutral salts: (a) Ham-

31. Gottwalt: (Reference given by Limbeck incorrect.) Correct reference, *Ztschr. f. phys. Chem.*, 1880, iv, 423, 427.

32. Vadala: *Clinica med. ital.*, 1907, vi; reference from *Biol. Centralbl.*, 1907, vi, No. 2480.

33. Grenet, H.: *Compt. rend. Soc. de biol.*, 1907, lxiii, 552.

34. Gilbert and Chiray: *Compt. rend. Soc. de biol.*, 1907, lxiii, 487.

35. Epstein: *Jour. Exper. Med.*, 1912, xvi, 719; *ibid.*, 1913, xvii, 444; *ibid.*, 1914, xx, 334.

mersten's method utilizes magnesium sulphate after which the precipitate is washed, dried and weighed, or the nitrogen in the precipitate is estimated by the Kjeldahl³⁶ method and the protein obtained by multi-

TABLE 4.—ALBUMIN AND GLOBULIN CONTENT OF HUMAN BLOOD SERUM IN CASES OF SYPHILIS *

Case	Clinical Diagnosis	Wassermann	Treatment	Serum Examination				
				Albu- min	Glob- ulin	Total Pro- tein	Non- pro- tein	Glob- ulin %
1	Chaneroid	Negative	None	6.4	1.2	7.6	1.1	16
2	Early secondary	Spirochetes demonstrated	None	5.3	2.3	7.6	1.1	30
3	Early malignant	+++	None	4.6	3.3	7.9	1.35	42
4	Early secondary	+++	None	5.4	2	7.4	1.3	27
5	Early secondary	+++	None	6.1	2.2	8.3	1.35	27
6	Tertiary	+++	Irregular for 2 yrs.	4.8	2.6	7.4	1.2	35
7	Early secondary	+++	2 Hg infec- tions	5.8	2.2	8	1.3	27.5
8	Early secondary	+++	None	3.7	3.6	7.3	1.2	49
9	Tertiary	+++	2 doses saliv.	4.7	2.6	7.3	1.25	36
10	Early secondary	+++	1 dose saliv. and Hg pills	4.2	2.7	6.9	1.2	40
11	Tertiary	++	1 dose	4.6	2	6.6	1.2	30
12	Gastric ulcer (no evi- dence of lues)	Faintly +	None	5.7	1.2	6.9	1.1	17
13	Tertiary aneurism	+++	None	4.6	2.5	7.1	1.5	35
14	Secondary	+++	None	5.2	2.9	8.1	1.3	36
15	Late—6 yrs.	+	None	4.5	2.9	7.4	1.4	39
16	Early secondary	+++	1 dose saliv. and Hg pills	5.5	2.4	7.9	1.4	30
17	Secondary	+++	Hg pills for 1 week	5.3	2.6	7.9	1.3	33
18	Late secondary	+++	Slight	5.4	1.9	7.3	1.4	26
19	Late secondary	+++	Saliv. and Hg	5.6	2.5	8.1	1.4	31
Averages.....				5	2.5	7.5	1.3	33.7

* Cases 1 and 12 were not used to obtain average values. All but three of these cases came from the South Medical department. Dr. O. Morton Smith furnished the diagnosis.

plying the nitrogen content by 6.25, as advised by König and Kisch.³⁷ The latter technic was described by Hoppe-Seyler.³⁸ (b) Hofmeister,³⁹ Pohl,⁴⁰ Kauder,⁴¹ and Reye⁴² used ammonium sulphate. Otherwise the method is the same as the former one.

36. Kjeldahl: Ztschr. f. anal. Chem., 1883, xxii, 366.

37. König and Kisch: Ztschr. f. anal. Chem., 1889, xxviii, 193.

38. Hoppe-Seyler: Handbuch der phys. u. path. chem. Analyse, 1893.

39. Hofmeister: Ztschr. f. phys. Chem., xx, 319.

40. Pohl: Arch. f. exper. Path. u. Pharmakol., 1886, xx, 426.

41. Kauder: Arch. f. exper. Path. u. Pharmakol., 1886, xx, 411.

42. Reye: Inaug. Diss., Strassburg, 1898.

There has been great divergence of opinion about the accuracy of these methods, well explained by Nellis Foster.⁴³ Howell⁴⁴ states that the precipitate of globulin by ammonium sulphate is unsatisfactory because of the changed properties of the globulin after precipitation. Robertson's method, in utilizing ammonium sulphate, thus carries with it some unavoidable objections. Still these objections are the same in all instances and thus deductions can safely be drawn from values obtained from pathologic cases. But in doing away with the evident sources of error arising from the complicated technic of the older methods and in utilizing small amounts of blood, Robertson's method is undoubtedly the most satisfactory one yet suggested. An experience of one year with the technic has shown me that uniform results are obtained, which, though they are much lower in globulin than former results, are thought to be dependable. The cause of this difference from former results will be investigated later.

The results given in literature for the total proteins have been more uniform than those for albumin and globulin. The refractometer was introduced by Strubell in 1900 to determine quantitatively the serum proteins, the method being perfected by Reiss in 1902. Since then many data dealing with total protein in human serum have been added to literature, the chief workers having been Achard, Ascher, Bohme, Chiray, Chajes, Engel, Koranyi, Bence, Luthje, Oppenheimer, Schwenker, Strauss, Widai and Vaucher. References to all this work done with the refractometer are given in the comprehensive article recently published by Reiss.⁴⁵ The results are in most points like those arrived at by former methods.

In 1913 Schorer⁴⁶ studied Reiss' refractometric method and concluded that the changed relation between albumin and globulin in disease gives rise to a definite error in estimating the total protein. This was because the refractive index of albumin is less than that of globulin as determined by Reiss, Robertson, and confirmed by Schorer. That the total protein as estimated by the Kjeldahl-Kolben method, or by precipitation by alcohol and weighing, agreed within a few tenths of 1 per cent. with the refractometric estimation was the result of work done by Reiss,⁴⁷ Widai and Laudat, and Tuffier and Maute.⁴⁸ Chiray and Démanche⁴⁹ and also Schorer⁵⁰ had been unable to obtain such

43. Foster, N.: *THE ARCHIVES INT. MED.*, 1912, x, 415.

44. Howell: *Am. Jour. Physiol.*, 1906, xvii, 280.

45. Reiss: *Ergebn. d. inn. Med. u. Kinderh.*, 1913, x, 531.

46. Schorer: *Cor.-Bl. f. schweiz Aerzte*, 1913, xlvii, 1523.

47. Reiss: *Ztschr. f. Electrochemie*, 1908, xiv, 613.

48. Tuffier and Maute: *Tribune med.*, Paris, 1905.

49. Chiray and Démanche: *Compt. rend. Soc. de biol.*, 1907, lxiii, 235.

50. Schorer: *Ueber refraktometrische Pepsin bestimmungen*, Diss., Bern, 1908, p. 22.

agreement of results, there being a difference of 1.8 per cent. in one of their results.

Using Reiss' table for the determination of total serum protein, Schorer shows plainly the source of error involved in the former's method.

The protein content of an assumed serum may be supposed to be 8 per cent. If Hammarsten's relation between albumin and globulin is used, then for one part of globulin there is one and a half parts of albumin and 8 per cent. protein would contain 3.2 per cent. globulin and 4.8 per cent albumin.

Refractive index of 1% albumin	= .00184 or 4.8% = ...	0.00883
Refractive index of 1% globulin	= .00230 or 3.2% = ...	0.00736

Refractive index of total protein	=	0.01619
Refractive index of distilled water	=	1.33320
Refractive index of nonprotein	=	0.00277

Hence the refractive index of whole serum = 1.35216

But the refractive index of a serum containing 8% protein according to Reiss' table = 1.3490. Error = 0.0026 or 1.4% protein.

If my average values given in this article for albumin, globulin and nonprotein are substituted for those of Reiss in the above calculations, one obtains an error of about 0.5 per cent. protein, if Reiss' table is used to determine the total protein directly from the refractive index. This error would increase as the globulin and nonproteins increased in disease.

Besides this error there is one due to the too large value for nonproteins adopted by Reiss. This has already been explained in a former paper.† The slight increase in the nonproteins found in the normals in this communication over the value in the former series of normals decreases the percentage of error to approximately 0.4 per cent. instead of 0.5 per cent., which results from the use of the constant value of 0.00277 for nonproteins as advised by Reiss.

It is evident, therefore, that there are two sources of error in the method of Reiss for the estimation of total protein in serum, both of which are removed by Robertson's method. In pathologic cases in which it is known that the nonproteins are not decidedly increased the average value for them given in this paper can be used. If this is done an error of 0.2 per cent. in the albumin content may occur. For clinical work such an error could be allowed, since the technic is greatly shortened if the nonproteins are not estimated in a given serum.

Reiss⁵¹ in his last article acknowledges the correctness of Schorer's criticism, but says that his method is of use in forming a serum pro-

† Footnote 63.

51. Reiss: *Deutsch. Arch. f. klin. Med.*, 1915, cvii, 175.

tein curve for a given patient, by estimating the protein each day, which yields valuable information, especially when combined with the curve of the body weight. He admits that his method is useless in uremia, because of the increase in nonproteins and globulins which occurs in this condition. With Robertson's method, on the contrary, it is entirely possible to make correct determinations of the total protein, albumin, globulin, and nonproteins of uremic serum. This has been done and the results will be published in a separate paper, in which the albumin and globulin content of serums in chronic diseases will be considered.

SYPHILIS

The serum proteins in syphilis have met with considerable attention. Jolles and Oppenheim⁵² found no difference in the protein content of normal and syphilitic serum. Klausner⁵³ was able to demonstrate an increase in the globulin in syphilitic serum by obtaining an abnormal precipitate when distilled water was added to such a serum. Sachs and Altmann⁵⁴ thought the Wassermann reaction was due to increased globulin, obtaining their precipitate with weak alcohol. Elias, Neubauer, Porges and Salomon⁵⁵ thought the active substance causing the Wassermann reaction belonged to the globulins and that they were present in greater amount in syphilitic than in normal serums. Noguchi⁵⁶ found globulin was increased in syphilis and thought it ran so nearly parallel to the Wassermann test that he, for a time, suggested it as a test for syphilis. His estimations were made by direct weighing of the moist globulin precipitate after centrifugalization at five thousand revolutions per minute for a definite time. Gay and Fitzgerald⁵⁷ were unable to obtain as definite results as did Noguchi and had better success with the quantitative estimation of euglobulin as a test for syphilis, than with the entire globulin fraction. Muller and Hough⁵⁸ found that syphilitic serums showed an increase in the euglobulin, but could establish no relation between the increase in globulin and the Wassermann reaction. Winternitz,⁹ by using the method of Hofmeister, Pohl, and Reye, found an increase in the euglobulins in a short series of syphilitics as well as an increase in the total globulins. Moreover, by using the refractometer he demonstrated an increase in the fibrinogen in syphilis. To estimate fibrinogen, he took the difference between the reading of the plasma obtained

52. Jolles and Oppenheim: *Ztschr. f. Heilk.*, 1903, xxiv, 105.

53. Klausner: *Wien. klin. Wchnschr.*, 1908, xxi, 214, 363.

54. Sachs and Altmann: *Berl. klin. Wchnschr.*, 1908, xiv, 522.

55. Elias, Neubauer, Porges and Salomon: *Wien. klin. Wchnschr.*, 1908, xxi, 748, 831.

56. Noguchi: *Jour. Exper. Med.*, 1909, xi, 84.

57. Gay and Fitzgerald: *Boston Med. and Surg. Jour.*, 1909, clx, 157.

58. Muller and Hough: *Wien. klin. Wchnschr.*, 1911, xxiv, 167.

by the use of hirudin and the reading of the serum. This difference he showed by quantitative chemistry was almost entirely due to fibrinogen.

In the series of nineteen cases in Table 4 the average value for globulin is definitely increased over the normal value, while that for nonprotein is very slightly increased. In Case 1, in which the clinical diagnosis of the early lesion was chancre, the percentage of globulin was found to be normal and the nonspecific nature of the lesion was confirmed by three subsequently negative Wassermann reactions. Cases 3, 6, and 8 were particularly severe and their globulin values

TABLE 5.—ALBUMIN AND GLOBULIN CONTENT OF HUMAN BLOOD SERUM IN PNEUMONIA

Case No.	Date	Diagnosis and Day of Disease	Wassermann	Serum Examination				
				Albumin	Globulin	Total Protein	Non-protein	Globulin %
1	1/19	Pneumonia, third day.....	Neg.*	3.6	2.7	6.3	1.4	43
2	1/10	Pneumonia, chronic endocarditis	Neg.
2	1/17	Wk.*	3.8	1.4	5.2	1.4	27
3	1/18	Pneumonia, eighth day.....	Neg.*	3.7	2.3	6	1.5	33
4	1/24	Bronchopneumonia, ninth	Wk.	3.1	2.5	5.6	1.5	45
	2/ 3	Neg.
5	1/20	Pneumonia, fourth day.....	Mod.
	1/24	Wk.*	3.9	2.4	6.3	1.6	38
6	1/28	Pneumonia unresolved with arthritis, thirtieth day	Neg.	3.6	3.5	7.1	1.2	49
7	1/28	Pneumonia, third day.....	Neg.	4.7	2	6.7	1.3	30
8	1/31	Pneumonia, delayed resolution tenth day	Neg.*	3.1	3.1	6.2	1.3	50
Averages.....				3.7	2.5	6.2	1.4	40

* Wassermann reactions were done on a sample of the same serum used for estimation of serum proteins.

were found to be among the highest in the series. Unlike other infections considered in this paper, there was no definite decrease in the total proteins.

PNEUMONIA

The literature reviewed in the first part of this paper shows a general agreement over the fact that globulin is increased in pneumonia. Sandelowsky,⁵⁹ moreover, has pointed out that the total serum protein falls during the fever and rises gradually during convalescence. An

59. Sandelowsky: Deutsch. Arch. f. klin. Med., 1909, xcvi, 445; *ibid.*, 1910, c, 324.

investigation of the cause of this fall convinced the latter that two types of cases existed:

First, we have those in which the weight remained stationary or increased during fever, decreasing after the fever, while the serum proteins decreased during the fever due to an increase in the water content of the body. Along with this increase in fluid there is a retention of salts, which keeps the osmotic pressure constant and helps to explain the diminished salt in the urine. It was found that only small amounts of salt were contained in the stool and sputum of pneumonic patients and that the supposition that pneumonic exudate contained more salt than normal was not true.

TABLE 6.—ALBUMIN AND GLOBULIN CONTENT OF HUMAN BLOOD SERUM IN INFECTIONS OTHER THAN SYPHILIS AND PNEUMONIA

Case No.	Diagnosis	Wassermann	Serum Examination				
			Albumin	Globulin	Total Protein	Non-protein	Globulin %
1	Lung abscess.....	Neg.*	4.2	3.9	8.1	1.2	48
2	Septic knee.....	Neg.	3.8	3.4	7.2	1.5	47
3	Pyelitis.....	Neg.	4.7	2.2	6.9	1.4	32
4	Infected compound fracture.....	Neg.	4.5	2.1	6.6	1.3	33
5	Recent empyema; acute nephritis....	Neg.	3.6	3.4	7	1.6	49
6	Acute mastoiditis; acute nephritis...	Neg.	3.1	2.1	5.2	1.5	40
7	Erythema nodosum.....	Weak+	4	4	8	1.45	50
8	Acute and chronic endocarditis; secondary anemia	Neg.	3.7	2.7	6.4	1.2	42
9	Malignant endocarditis.....	Neg.	3.8	3.4	7.2	1.5	47
10	Chronic endocarditis; acute arthritis	Neg.	5.7	3.1	8.8	1.3	35
11	Chronic sepsis.....	Neg.	4.4	2.7	7.1	1.3	38
12	Acute tonsillitis.....	Neg.	5.8	2.2	8	1.2	27.5
13	Chronic bronchitis.....	Neg.	5.7	2	7.7	1.3	26
14	Tuberculosis of pleura.....	Neg.	4.8	2.9	7.7	1.3	33
15	Typhoid, tenth day; Widal +.....	Neg.	5.4	1.9	7.3	1.3	26

* Wassermann reaction was done on a sample of the serum used for estimation of serum proteins.

Second, we have those in which weight dropped during fever and rose afterwards, while the serum proteins were reduced during the febrile period. Here the consumption of tissues must be accepted as the main cause for the reduced proteins.

The cause for this water and salt retention was thought to be kidney damage, caused mainly by toxins and not caused by fever in itself. Sandelowsky in a later article showed that by producing fever artifi-

cially in dogs the serum proteins were reduced, due to an increase in water in the blood, which he considered possibly a biologic reaction provided against overheating of the body.

Achard, Touraine and Saint-Girons⁶⁰ found that in pneumonia, as well as in typhoid, paratyphoid, acute rheumatic fever, phlegmonous sore throat, and streptococcic septicemia, the serum concentration falls until the fever ceases, in some cases, especially in typhoid, to a point higher than normal, after which it drops to the normal level. The most pronounced decrease occurred with typhoid and pneumonia, while only a small decrease came in slight infections.

The results of the examinations in pneumonic serum, as given in Table 5, show a more definite increase in the percentage of globulin than syphilis. The total proteins are decreased moderately, due probably to edema, while the nonproteins are slightly increased. Comment on the accompanying Wassermann reactions will be made in the last section of this paper.

INFECTIONS OTHER THAN SYPHILIS AND PNEUMONIA

The summary of literature under pneumonia applies in large part to the infections to be considered in this section. Though no serum from scarlet fever was examined, it is interesting to include a note about the work of Oppenheimer and Reiss,⁶¹ who showed that the serum proteins decreased, while the body weight increased, during the febrile period. A salt retention was found in this disease, as well as in pneumonia. An attempt was made to determine the presence of nephritis, before the usual signs and symptoms appeared, by following the serum proteins, but without any definite success. Kalser and Löwy⁶² found that serum proteins increased after the febrile period, but since they followed no case during the entire febrile period, their conclusion that the serum in scarlet fever is not diluted during the febrile period is not justified.

Most of the cases in Table 6 were of rather medium severity or of considerable duration. It is seen that the total proteins are higher than in cases of pneumonia, though the percentage of globulin is as high. The nonproteins are slightly increased.

Case 5 was one of empyema with little fever and an acute nephritis, with edema confined to the groins. The blood serum is not diluted, though the globulins are markedly increased. If these results are compared to those in Case 6, which was similar except that general edema was present, due to greater kidney damage, as shown by the high

60. Achard, Touraine, and Saint-Girons: *Arch. de med. expér. et d'anat. path.*, 1912, xxiv, 647.

61. Oppenheimer and Reiss: *Deutsch. Arch. f. klin. Med.*, 1909, xcvi, 464.

62. Kalser and Löwy: *Deutsch. Arch. f. klin. Med.*, 1914, cxiv, 82.

TABLE 7.—EFFECT OF THE INCREASE OF GLOBULIN BY VENOUS STASIS ON THE WASSERMANN REACTION

Case No.	Diagnosis	Normal Serum					Serum after Venous Stasis						
		Albumin	Globulin	Total Protein	Nonprotein	Percentage Globulin	Wassermann	Albumin	Globulin	Total Protein	Nonprotein	Percentage Globulin	Wassermann
1	Obstructive jaundice.....	3.8	2.5	6.3	1.25	40	Mod.	4.7	3.4	8.1	1.3	42	Mod.*
2	Enlarged inguinal glands ?	1.7	2.4	7.1	1.35	34	Neg.*	7	3.4	10.4	1.45	33	Neg.
3	Septic knee.....	3.8	3.4	7.2	1.5	47	Neg.*	5.2	4.2	9.4	1.5	45	Neg.*
4	Aortitis (syphilitic ?); arteriosclerosis; bronchopneumonia; secondary anemia	4.4	3.7	8.1	1.3	46	Neg.*†	5	4	9	1.3	44	Neg.*
5	Normal.....	5.1	1.7	7.1	1.2	24	Neg.*	5.8	2.1	7.9	1.2	27	Neg.*
6	Chronic nephritis.....	3.9	2.1	6.3	1.8	38	Neg.*	5.3	3.4	8.7	1.8	39	Neg.*

*Wassermann reactions were done on a sample of the same serum used for estimation of serum proteins.

† Five days before this examination Wassermann was weak positive. Patient was given mercury and iodid after that time.

value for nonproteins as well as a high nonprotein nitrogen, the effect of increased fluids in the blood is well demonstrated.

Case 12 was one of ordinary tonsillitis of about three days' duration. The values are normal. Case 14 shows a moderate increase in the percentage of globulin, which agrees with the findings of Erben referred to in the first part of this paper. Because of the season of year, only one typhoid serum was examined. The low globulin content is interesting and, if confirmed, will suggest the possibility that increased leukocytes have something to do with increased globulin, as suggested by A. Schmidt, to which suggestion Hammarsten called attention, or that the globulin has a greater resistance to destruction by toxins than has albumin, as suggested by Gottwald.⁶¹

RELATION OF SERUM GLOBULINS TO THE WASSERMANN REACTION

Literature, as reviewed in the section on syphilis, shows the association that serum globulin has been assumed to have with the Wassermann reaction. But attempts to use the globulin content as a test for syphilis have proved fruitless.

The data which are given in Tables 7 and 8 emphasize the fact that the Wassermann reaction does not depend on a quantitative increase in the serum globulins.

In Tables 4, 5 and 6 the results of the Wassermann reaction, as done in Dr. Wright's laboratory at the Massachusetts General Hospital, are given. The main point of interest is that serums showing a strongly positive test contained on the average considerably less globulin in relation to the total protein than did some showing a negative reaction.

In Tables 5 and 6 several weakly positive Wassermann reactions occurred without any history or any manifestations of syphilis. They were probably examples of spurious reactions, which are known to occur in severe infections. In Case 4 of Table 5 the weak positive became negative during convalescence.

In a recent article the writer⁶³ has shown that with venous stasis the serum globulin and albumin are proportionately increased. In Table 7 venous stasis has been used to determine whether an actual increase in the globulin content of a serum would increase or cause a positive Wassermann reaction. Wassermann reactions were done on samples of the same serums used in determining the serum proteins. The results show that an absolute increase of 1 per cent. of globulin does not change the results of the fixation test.

Minot and Sellards⁶⁴ have shown that negative serums exert an antagonistic action on the Wassermann reaction. The amount of this

63. Rowe, A. H.: *Jour. Lab. and Clin. Med.*, 1916, i, 485.

64. Minot and Sellards: *Jour. Med. Research*, 1916, xxxiv, 131.

antagonistic reaction can be determined by combining a definite amount of the negative serum with the minimal amount of a positive serum which causes complete fixation, after which a Wassermann test is done. When no antagonistic action is present in the negative serum, no hemolysis occurs, and when such an action is present, hemolysis takes place, up to an absolutely complete degree when the inhibitory power of the negative serum is great. The possibility of studying

TABLE 8.—RELATION OF GLOBULIN TO THE INHIBITORY POWER OF SERUMS TOWARD THE WASSERMANN REACTION *

Case No.	*Diagnosis	Globulin	Percentage Globulin	Hemolysis
1	Syphilis.....	1.4	18	0
2	Syphilis.....	2.3	34	0
3	Late syphilis.....	4.8	45	0
4	Syphilis.....	2.1	27	0
5	Chronic bronchitis (history of 5 miscarriages)	1.0	29	0
6	Endocarditis; arthritis.....	3.1	35	0
7	Cholecystitis; syphilis (?).....	2.3	33	T
8	Colloid goiter.....	1.8	28	T
9	Goiter hyperthyroidism.....	1.1	16	T
Averages.....		2.3	29.4	...
10	Chronic cholecystitis.....	2.5	35	P
11	Normal.....	1.9	29	P
12	Diabetes.....	2.3	29	P
13	Phthisis; pleurisy.....	2.9	38	AC
14	Cardiac.....	1.9	30	AC
15	Goiter; hyperthyroidism.....	2	27	C+++
Averages.....		2.25	31.3	...

* All serums in this table were negative to the routine Wassermann reaction. In this table 0 signifies no hemolysis; T, trace of hemolysis; P, partial hemolysis; AC, almost complete hemolysis; C, complete hemolysis.

doubtful negative reactions with this method is evident. Friedemann⁶⁵ was able to obtain a positive Wassermann reaction with normal serum globulin, while normal serum albumin prevented fixation. He thought that in normal serum the albumin protects against fixation, while in syphilitic serum the albumin has no such power. Zinsser,⁶⁶ in discussing the Wassermann reaction, reviews the work of Schmidt, who

65. Friedemann: Ztschr. f. Hyg. u. Infektionskrankh., 1910, lxxvii, 279.

66. Zinsser: Harvey Lectures, 1914-1915, 178: Infection and Resistance, 1915.

states that globulin in syphilitic serum is increased quantitatively and is changed qualitatively and that it probably unites directly with the extract colloids in the antigen of the Wassermann test.

The writer, at the suggestion of Drs. Minot and Sellards, has estimated the globulin in serums on which they had tested the inhibitory power toward the Wassermann reaction. The minimal amount of a positive serum (0.005 c.c. in these cases) which caused complete fixation was added to 0.1 c.c. of each serum tested and a Wassermann reaction was done on each specimen with the results shown in Table 8. It was hoped that a diminution in globulin would occur in serums which inhibited the Wassermann reaction, whereas a high globulin content would be found in those in which no inhibitory power was present.

The results in Table 8 show an average value of 29.4 per cent. for the globulin in serums causing a trace or no hemolysis, while the average of the values in serums with partial, almost complete, and complete hemolysis is slightly higher, being 31.3 per cent. More estimations on serums causing complete hemolysis must be made before any definite conclusions can be drawn as to whether all serums showing complete hemolysis will have low globulin content.

The data given in the last section of this article lead to the conclusion that the Wassermann reaction is not due to a quantitative increase in the serum globulins.

SUMMARY

A series of normal cases shows that serum albumin varies between 4.6 and 6.7 per cent., that globulin varies between 1.2 and 2.3 per cent., that total proteins vary between 6.5 and 8.2 per cent., that nonproteins vary between 1.1 and 1.3 per cent., while the percentage of globulin in the total protein varies from 16 to 32 per cent. The average value for albumin was found to be 5.6 per cent. for globulin, 1.9 per cent., for total protein 7.5 per cent., for nonprotein 1.24 per cent. and for globulin 25.5 per cent.

The normal values for total protein, albumin and globulin from the entire literature are given, while the literature on these proteins in health and disease as well as on methods of their estimations is summarized.

The former use of the refractometer in medical research is discussed, while the error in Reiss' method for the determination of total proteins is pointed out. It is shown that Robertson's microrefractometric method for the determination of total protein is free from evident error and for the estimation of albumin and globulin is the most satisfactory method yet proposed.

In syphilis the globulin is definitely increased, while the total protein remains about normal.

In pneumonia the globulin is increased more in relation to the total protein than in syphilis, while the total protein is reduced, due, probably, in large measure to a dilution of blood serum by water retention, which occurs in fever.

In many chronic septic conditions, in mild infections and typhoid, the total protein is not decreased, as it is in pneumonia. Globulin seems definitely increased in all infections, except in acute tonsillitis, typhoid, and in certain mild infections, such as chronic bronchitis. The marked dilution of serum which occurs with anasarca is shown in two cases of acute infection associated with acute nephritis, which were investigated.

The evidence presented shows that the Wassermann reaction is not due to a quantitative increase in the serum globulins.

I wish to express my sincere gratitude to Drs. Edsall and Dennis for advice given during this research. I also appreciate the opportunity of using the ward cases on the services of Drs. Lee, Lord, Pratt, and William Smith, and the cases in the outpatient departments of Drs. Richard Cabot and C. Morton Smith.

THE BLOOD PLATELETS IN HEMOPHILIA *

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Hemophilia on account of its striking nature was early recognized as a clinical entity, and has been the subject of many observations. Many theories as to its causation have been advanced. With the development of methods for the study of the blood it has been possible to discard most of the theories concerning this interesting disease.

It has been conclusively shown that in typical cases the numerical counts of the formed elements of the blood, the erythrocytes and the leukocytes are within normal limits. The blood platelets may be somewhat increased. It has also been shown in typical cases that certain active principles of the blood that participate in clotting occur in normal amounts. The hemophilic blood serum¹ contains the normal amount of thrombin, the active coagulating principle, and this thrombin behaves in an entirely normal fashion. It has further been shown that the hemophilic blood clot, when once formed, is as tough and firm as normal and retracts in normal fashion. The fibrinogen² and calcium³ are considered to be within normal limits.

It has been suggested that the presence of an excess of some anti-coagulating substance was the cause for the long coagulation time exhibited by hemophilic blood. Weil⁴ has given some experimental evidence that an excess of antithrombin occurs in hemophilic blood. Howell,⁵ however, was not able to find that his antithrombin was notably increased in hemophilia. The findings of Hurwitz and Lucas,⁶ Hess⁷ and our studies confirm Howell's findings in regard to antithrombin.

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* From the Pathological Laboratory, J. H. Wright, director, and the Medical Service of the Massachusetts General Hospital.

1. Fonio: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1914, xxviii, 313. Addis: *Jour. Path. and Bacteriol.*, 1911, xv, 427. Gressot: *Zeschr. f. klin. Med.*, 1912, lxxvi, 194. Morowitz and Lossen: *Deutsch. Arch. f. klin. Med.*, 1908, xciv, 110.

2. Addis: *Jour. Path. and Bacteriol.*, 1911, xv, 427. Sahli: *Ztschr. f. klin. Med.*, 1905, lvi, 264; *Deutsch. Arch. f. klin. Med.*, 1910, xcix, 518. Hurwitz and Lucas: *THE ARCHIVES INT. MED.*, 1916, xvii, 543.

3. Addis: *Jour. Path. and Bacteriol.*, 1911, xv, 427. Nolf: *Ergebn. d. inn. Med. u. Kinderh.*, 1913, x, 275. Morowitz and Lossen: *Deutsch. Arch. f. klin. Med.*, 1908, xciv, 110. Hess: *Bull. Johns Hopkins Hosp.*, 1915, xxvi, 372.

4. Weil: *Bull. et mém. Soc. méd. hôp. de Paris*, 1906; *Presse méd.*, 1905, xiii, 673.

5. Howell: *THE ARCHIVES INT. MED.*, 1914, xiii, 76.

6. Hurwitz and Lucas: Footnote, 2, last reference.

7. Hess: *THE ARCHIVES INT. MED.*, 1916, xvii, 203.

Morawitz and Lossen⁸ and Sahli⁹ are inclined to attribute the faulty coagulation to an insufficiency or defective formation of the element known in various terminologies as thrombokinese, thromboplastic substance,¹⁰ tissue juice, cytozyme or thrombozyme. This is similar to the view of Nolf and Herry,¹² who believe that there is a quantitative or qualitative deficiency in the thrombozyme, which occurs in the blood platelets in the circulating blood in contrast to the similar factor in the tissues. These various substances mentioned above are not exactly identical in the various terminologies, but can be considered roughly comparable and are found in the blood platelets and tissue juices. The action ascribed to them varies according to the theories of coagulation; all theories hold in common that they accelerate the coagulation of the blood.

Addis¹³ believes that the abnormality of hemophilic blood is to be found in the property of the prothrombin, that it is altered in character so that it requires a longer time than normal for its activation to thrombin. Howell⁵ concludes from his experiments that it is the actual amount of prothrombin that is altered in the hemophilic blood and is inclined to believe that it is the deficiency in the amount of prothrombin with the resulting relative excess of antithrombin that is responsible for the abnormally long coagulation time. He does not deny to the blood platelets a share in this deficiency.

The action of blood platelets from cases of hemophilia has received but little study and forms the basis of this paper.

Fonio,¹⁴ who believes that the active coagulating principle in the tissues, while similar, is not identical with that of the blood platelets, is inclined to attribute the delayed coagulation in hemophilia, from the study of one case, to an insufficiency of thrombozyme or blood platelets, which are present in sufficient amounts. Sahli¹⁵ in 1910 demonstrated similar differences with hemophilic and normal red blood cells as Fonio did with platelets. His results, perhaps, were due to platelets contained in his red cell suspensions. Addis¹⁸ has discussed Sahli's results.

The experiments given below were made with the blood platelets obtained from two typical cases of hemophilia and show clearly that hemophilic platelets do not act like normal platelets. The platelets of a third case of hemophilia, a mild case, gave the same, but less striking, results.

8. Morawitz and Lossen: Footnote 1, last reference.

9. Sahli: Footnote 2, second reference.

10. Howell: *Am. Jour. Physiol.*, 1912-1913, xxxi, 1.

12. Nolf and Herry: *Rev. de méd.*, 1909, xxix, 841; 1910, xxx, 20 and 106.

13. Addis: Footnote 1, second reference.

14. Fonio: *Cor.-Bl. f. schweiz. Aerzte*, 1915, xlv, 1505; Footnote 1, first reference.

15. Sahli: Footnote 2, second reference.

METHODS

Plasma was obtained from the hemophilic blood without adding any oxalate or other foreign substance, by drawing the blood from the arm vein into a paraffined syringe and centrifugalizing it, by preference, in iced paraffined tubes. A clear plasma containing very few platelets could easily be obtained, which did not clot for twelve hours. The cloudier the plasma, that is, the more platelets it contained, the quicker it clotted. Platelet suspensions in normal salt solution were obtained from the "buffy coat" and from the cloudy plasma of the hemophilic blood by the usual technic described first by Mosen¹⁶ and later modified by us.¹⁷ Platelets were obtained also from the cloudy plasma and "buffy coat" of oxalated, citrated, and magnesium sulphate normal and hemophilic plasmas. The results with the hemophilic platelets were essentially the same irrespective of the particular method of obtaining them or the number of washings. The same was true of the normal platelets.

ACTION OF PLATELETS ON HEMOPHILIC PLASMA

The effect of adding suspensions of hemophilic and normal platelets to hemophilic plasma is shown in Tables 1, 2 and 3.

Hemophilic plasma clots most rapidly on the addition of normal platelets. Roughly, the time varies inversely to the number of platelets. Yet an increase of platelets above a certain amount, relatively small, does not greatly shorten the time. Hemophilic platelets hasten somewhat the clotting of hemophilic plasma, although nowhere nearly as markedly as normal platelets in the same concentration. In each instance the clotting time of the mixture of hemophilic plasma and hemophilic platelets in any concentration of platelets is always markedly longer than the clotting time of the mixture of hemophilic plasma and normal platelets. Even when the mixture contains seventy-five times as many hemophilic platelets as ordinarily occur in the circulating blood, the clotting time of the mixture is abnormal and markedly longer than the clotting time of a mixture of hemophilic plasma and normal platelets in which the platelets are approximately in the same number as in the circulating blood. The same results were obtained whether the platelets from one hemophilic case were added to its own or to another hemophilic plasma. The platelets obtained from the hemophilic case with the longest coagulation time usually, but not always, required a somewhat longer time to cause a hemophilic plasma to clot than those from the case with the shorter coagulation time. An example of this is given in Table 3. These studies were repeated many times.

16. Mosen: Arch. f. Anat. u. Physiol., 1893, Physiol. Abst., p. 352.

17. Lee and Vincent: THE ARCHIVES INT. MED., 1914, xiii, 398.

TABLE 1.—EFFECT OF ADDING HEMOPHILIC AND NORMAL PLATELETS TO HEMOPHILIC PLASMA

Strength of Platelet Suspension	Variety and Amount of Platelet Suspension Added to 6 Gtt. of Hemophilic Plasma	Time Coagulation Begins, Minutes	Time for Solid Clot to Form, Minutes
Saturated.....	Normal 2 gtt.	4	6
	Normal 3 gtt.	4	5
	Hemophilic 2 gtt.	21	42
	Hemophilic 6 gtt.	13	23
Platelets about four times as concentrated as in blood.....	Normal 2 gtt.	5	8
	Normal 3 gtt.	5	7
	Hemophilic 2 gtt.	38	55
	Hemophilic 6 gtt.	38	55

TABLE 2.—EFFECT OF ADDING HEMOPHILIC AND NORMAL PLATELETS TO HEMOPHILIC PLASMA

Strength of Platelet Suspension	Variety and Amount of Platelet Suspension Added to 6 Gtt. of Hemophilic Plasma	Time Coagulation Begins, Minutes	Time for Solid Clot to Form, Minutes
About twice as concentrated as in blood {	Normal 3 gtt.	19	24
	Hemophilic 3 gtt.	77	120
About eight times as concentrated as in blood..... {	Normal 2 gtt.	18	22
	Hemophilic 2 gtt.	55	95
	Hemophilic 11 gtt.	52	85
About sixteen times as concentrated as in blood..... {	Normal 2 gtt.	16	21
	Hemophilic 2 gtt.	47	72
Saturated solid mass of pure white platelets..... {	Normal 2 gtt.	15	20
	Hemophilic 2 gtt.	50	76
	Hemophilic 10 gtt.	35	50

TABLE 3.—EFFECT OF ADDING TO THE SAME OR DIFFERENT HEMOPHILIC PLASMAS PLATELETS FROM TWO DIFFERENT CASES OF HEMOPHILIA *

Strength of Platelet Suspension	Variety and Amount of Platelet Suspension Added to 6 Gtt. of Hemophilic Plasma	Time Coagulation Begins, Minutes	Time for Solid Clot to Form, Minutes
Saturated.....	Hemophilic 1, 1 gtt.	54	70
	Hemophilic 2, 1 gtt.	41	70
	Hemophilic 1, 12 gtt.	48	65
	Hemophilic 2, 12 gtt.	20	35

* No. 1 had a shorter coagulation time than No. 2.

Usually, as shown in Table 1, the normal platelets allowed the hemophilic plasma to clot as rapidly as normal blood; occasionally the normal platelets did not shorten the time of a particular plasma quite so much (Table 2). This may have been due to a poor suspension of normal platelets, since it is possible that in collecting them some of their activity was destroyed. However, a heavy solution of cephalin (Howell's thromboplastic substance¹⁰) added to the hemophilic plasma acted similarly to the normal platelet suspension; that is, if the normal platelets in concentration could shorten the coagulation time of the hemophilic plasma only to twelve minutes, then cephalin could shorten it only to ten or twelve minutes; while if the normal platelet suspension shortened the coagulation time to four minutes, cephalic shortened it to three or four minutes. Such differences seem to have been due to differences in the plasma on the different days. It is possible that the difference was due to some slight alterations in the technic in collecting the blood which were not appreciated. A reasonable interpretation of this difference is the presence of some antagonistic substance in the plasma itself. This substance may be constantly present, but may have been detected only under favorable circumstances. It seems somewhat distinct from the platelets, but may be derived from them.

ACTION OF PLATELETS ON RECALCIFIED OXALATED PLASMA

The Effect of Adding Platelets to Hemophilic Recalcified Oxalated Plasma.—Table 4 shows the results obtained on adding normal and hemophilic platelets to hemophilic oxalated plasma and then adding varying amounts of calcium. This table shows that the normal platelets, even in small amounts, are able to accelerate the clotting time of recalcified oxalated hemophilic plasma more than hemophilic platelets, even when the latter are added in great concentration. This difference between the action of the hemophilic and normal platelets is quite similar to their different action seen when they were added to the unoxalated hemophilic plasma. It is to be noted that if one uses an optimum amount of calcium to recalcify the hemophilic oxalated plasma the difference between adding normal and hemophilic platelets is not so great as when the amount of calcium used is below the optimum. Also it is to be noted that the time of beginning coagulation in the presence of the hemophilic platelets may be nearly the same as in the presence of normal platelets when the optimum amount of calcium is used. However, the time from the appearance of the first fibrin strands to the point at which the clot is solid, is shorter when normal rather than when hemophilic platelets are added. The most striking results are seen when but little calcium is added. In such instances, when one adds one quarter as many normal as hemophilic platelets, a solid clot is formed some minutes before any coagulation is evident in the tube

containing four times as many hemophilic platelets, which never becomes solid. We interpret these results as follows: Under the most favorable conditions the hemophilic platelets act fairly well, but not so well as normal platelets. Under unfavorable conditions the hemophilic platelets act poorly and some of them probably not at all, so that not enough thrombin is formed or rendered available to complete coagulation.

TABLE 4.—EFFECT OF NORMAL AND HEMOPHILIC PLATELETS ON THE CLOTTING TIME OF RECALCIFIED HEMOPHILIC OXALATED PLASMA

Strength of Platelet Suspension Added	Variety and Amount of Platelet Suspension Added to 6 Gtt. of Hemophilic Oxalated Plasma	4 Gtt., 5% CaCl ₂		3 Gtt., 5% CaCl ₂		2 Gtt., 5% CaCl ₂	
		Coagulation Begins, Min.	Time for Solid Clot to Form, Min.	Coagulation Begins, Min.	Time for Solid Clot to Form, Min.	Coagulation Begins, Min.	Time for Solid Clot to Form, Min.
About four times as concentrated as in blood	Normal 2 gtt.	7	10	18	25	Sliding jelly clot, 30	Not in three hours
	Normal 5 gtt.	6	9	10	16	Sliding jelly clot, 25	Not in three hours
	Hemophilic 2 gtt.	8	16	30	Never	Never	Not in 3 hours
	Hemophilic 5 gtt.	8	15	17	36 (never firm)	Never	Not in 3 hours
Saturated.....	Normal 2 gtt.	4	7	5	7	7	11
	Hemophilic 2 gtt.	8	15	14	Sliding jelly clot 30, never solid	Never	Not in three hours
	Hemophilic 4 gtt.	8	15	14	Sliding jelly clot 30, never solid	Tiny strands 25	Not in three hours
	Hemophilic 8 gtt.	7	14	13	24, never as solid as with normal platelets	Weak sliding jelly, 19	Not in three hours
0	0	?	60	?	Never	?	Not in 3 hours

The Effect of Adding Platelets to Normal Oxalated Plasma.—Table 5 is similar to Table 4 and shows the effect of adding normal and hemophilic platelets to oxalated normal plasma, which is then recalcified. The difference between the action of the hemophilic and normal platelets on recalcified normal plasma is much more difficult to demonstrate than on hemophilic plasma, even using an amount of calcium below the optimum. Better results were obtained with a plasma that had stood forty-eight hours than with plasma a few hours old. With an optimum amount of calcium no especial difference could be

seen between the accelerating action of normal and hemophilic platelets. With an amount of calcium just below the optimum often there occurred no essential difference in the time that the clots formed in the presence of the two kinds of platelets. In general, the clotting time seemed a shade longer with hemophilic platelets. However, it was always noticed that the clots formed in the presence of the hemophilic platelets were at the time they were solid, distinctly of a weaker nature than those containing normal platelets. Later they became as firm as those with the normal platelets.

By using a suitable amount of calcium that could only be determined for each oxalated plasma by many trials we got the results given in Table 5, under two drops of calcium, where the difference between adding hemophilic and normal platelets is clearly demonstrated. Here, though coagulation at times began at about the same

TABLE 5.—EFFECT OF NORMAL AND HEMOPHILIC PLATELETS ON THE CLOTTING TIME OF RECALCIFIED NORMAL OXALATED PLASMA

Strength of Platelet Suspension	Variety and Amount of Platelet Suspension Added to 6 Gtt. of Normal Oxalated Plasma	Time in Minutes for Solid Clot to Form, with 5% Solution CaCl ₂ Added		
		4 Gtt.	3 Gtt.	2 Gtt.
About four times as concentrated as blood	Normal 1 gtt. Normal 5 gtt. Hemophilic 1 gtt. Hemophilic 5 gtt.	4 3+ 4+ 4	7 4— 10* 4+*	9 5+ Never Begins 10, never solid
Saturated.....	Normal 1 gtt. Hemophilic 2 gtt.	4— 4+*	4— 4+*	5 6+, never solid
0	0	8	Begins 9, never solid	Few strands 25, never solid

* Though solid at the time given, these clots were not so firm as those containing normal platelets and did not become any firmer.

time, no matter whether hemophilic or normal platelets were added, the latter allowed a solid clot to form, while the plasma with the hemophilic platelets never became solid. Thus the beginning coagulation time may be near the same time with either kind of platelets, while with hemophilic platelets the ending coagulation time is much delayed.

We assume that only under unfavorable conditions can marked differences be detected between the action of hemophilic and normal platelets on normal plasma. Ordinarily in oxalated normal plasma recalcification makes favorable conditions. As we shall bring out later, our microscopic studies show that hemophilic platelets under favorable conditions undergo transformation not very differently from normal platelets. Irrespective of any possible antagonistic substance in the hemophilic plasma, it is very different from normal oxalated plasma. Hemophilic plasma may well be compared to an oxalated normal

plasma collected by the most careful technic, as described previously by us.¹⁷ Such a plasma, in which the greatest care is exercised to prevent any of the changes incident to coagulation, will clot on recalcification with the optimum amount of calcium in forty minutes or more. Under the usual conditions of technic of preparing an oxalated plasma, the plasma will clot upon recalcification in fourteen minutes or less. Under the latter conditions the earlier changes incident to the process of coagulation have already begun and the plasma may be said to be partially prepared for clotting before recalcification. Hemophilic plasma can be readily obtained relatively free from these preliminary changes. On the other hand, normal plasma can be so obtained only by the exercise of special precautions. We have already shown elsewhere that these precautions in normal plasma result in the preservation of intact platelets. In hemophilic plasma the platelets, seemingly fixed, require no such elaborate precautions.

ABILITY OF HEMOPHILIC PLATELETS TO FORM THROMBIN ACCORDING TO
THE THEORY OF BORDET AND DELANGE

In order further to determine the difference between hemophilic and normal platelets the ability of each to form thrombin was tested. This was done according to Bordet and Delange's¹⁸ method. They believe that thrombin is formed by the reaction between cytozyme (platelets and other tissue juices) and serozyme (similar to prothrombin) in the presence of soluble calcium salt. Serozyme is the defibrinated serum obtained after a very clear oxalated plasma, free as possible from platelets, has been clotted by recalcification and kept for twenty-four hours to get rid of any active thrombin. Such a thrombin requires about six or seven minutes to form. The addition of oxalate to a mixture of platelets and serozyme and calcium not only precipitates the calcium and prevents the further formation of thrombin, but also has a deterrent effect on the thrombin.¹⁷ It is thus possible to demonstrate the amount and activity of a thrombin thus formed within any given time and furthermore to determine the rapidity with which thrombin is formed, since thrombin and fibrinogen react quantitatively to a certain degree, especially if dealing with minute amounts of thrombin.

Table 6 is a typical protocol of often-repeated experiments. For these experiments serozyme, thrombin-free platelets, calcium solution, and a fibrinogen solution were used. The serozyme was demonstrated to be free of active thrombin in that it did not clot the fibrinogen solution in twenty-four hours. The action of normal and hemophilic

18. Bordet and Delange: *Ann. de l'Inst Pasteur*, 1912, xxvi, 657 and 737.
Lee and Vincent: Footnote 17.

serozyme was the same. In the tests, to one drop of serozyme was added 0.5 c.c. of a 1 to 100 aqueous solution of calcium chlorid and then suspensions of platelets. The platelets were used in amounts over ten times the minimum required to form enough thrombin to clot the fibrinogen solution in three minutes. After the calcium, serozyme, and platelets had been in contact either six or eight minutes, varying amounts of a 1 per cent. solution of sodium oxalate were added to inhibit the action of forming more thrombin and to paralyze what thrombin had been formed. Then, either immediately or after an interval not exceeding four minutes a fibrinogen solution was added and the time a clot formed was noted. If there was an excess of thrombin formed, the effect of adding a small amount of oxalate did not alter the coagulation time with the fibrinogen solution. If a small amount of thrombin was formed, it paralyzed this small amount and delayed the reaction between thrombin and fibrinogen.

TABLE 6.—ABILITY OF NORMAL OR HEMOPHILIC PLATELETS TO FORM THROMBIN ACCORDING TO BORDET AND DELANGE'S METHOD *

Drops of Saturated Suspension of Platelets	Amount of 1% Solution of Sodium Oxalate Added, Gtt.	Clotting Time, Minutes
Normal $\frac{1}{4}$ or 1.....	0	3
Hemophilic $\frac{1}{4}$ or 1.....	0	3
Normal 1.....	$\frac{1}{2}$	3
Hemophilic 1.....	$\frac{1}{2}$	16
Normal 1.....	1	5
Hemophilic 1.....	1	32
Normal 1.....	2	25
Hemophilic 1.....	2	About $4\frac{1}{2}$ hours

* In each of the preparations there was 1 gtt. of serozyme and 0.5 c.c. of dilute (1 to 100) calcium chlorid solution, to which was added the amount of platelets indicated; then after an interval of six or eight minutes in each instance there was added the amount of oxalate solution given, then either immediately or after waiting not more than four minutes more 6 gtt. of a fibrinogen solution was added; clots forming in the time given.

By referring to Table 6 it is seen that a sufficient amount of hemophilic platelets can form enough thrombin to clot fibrinogen in the same time as thrombin formed by normal platelets, provided adequate time was given for the formation of thrombin. However, it is seen that by the addition of oxalate after thrombin has been formed, it takes a much longer time for the thrombin formed by the hemophilic platelets than by the normal platelets to clot the fibrinogen, even in some instances eighteen times as long. This is best explained by the fact that there is a slow formation of thrombin by the hemophilic platelets and that in the given time they have formed less thrombin. That

there is plenty of thrombin eventually formed has often been shown, since hemophilic serum contains fully as much thrombin as normal. We assume therefore that thrombin is formed more slowly.

To demonstrate further that these hemophilic platelets were slow thrombin formers we used varying dilutions of hemophilic and normal platelet suspensions. It was found that a thrombin formed with one drop of a very weak suspension of hemophilic platelets required a much longer time to clot fibrinogen than when an equal suspension of normal platelets was used. Similar results were obtained with weak, but more concentrated, suspensions. In such an experiment we deal with the great difficulty of making equal platelet suspensions and being able to say they are truly equal. Since the hemophilic blood contained more platelets and yielded platelets more easily, the error favored the hemophilic rather than the normal suspension. However, whether one

TABLE 7.—DIFFERENCE BETWEEN ADDING HEMOPHILIC PLATELET EXTRACT AND SUSPENSION TO HEMOPHILIC PLASMA

Amount of Hemophilic Plasma	Character of Suspension or Extract of Hemophilic Plates	Amount of Extract or Suspension Added, Gtt.	Coagulation Begins, Min.	Coagulation Intermediate, Min.	Coagulation Ends, Min.
6 gtt.	0	0	360	?	?
6 gtt.	1 gtt. of saturated suspension and 5 gtt. of salt solution	6	50	80	150
6 gtt.	1 gtt. of extract of same saturated suspension	3	12	20	30
	The same with 9 gtt. of water	6	10	17	26

uses a few platelets to form thrombin, or allows a large number of platelets to form what thrombin they can and then this is paralyzed by oxalate, one arrives, of course, at the same results. The actual experimental results are the same and show that the hemophilic platelets act much more slowly in forming thrombin than normal platelets.

In these experiments the fibrinogen solution used consisted of one part oxalated plasma, eight parts 0.9 per cent. salt solution and 0.5 part of 1 per cent. sodium oxalate in 0.9 per cent. sodium chlorid. Both hemophilic and normal oxalated plasma were used. If hemophilic fibrinogen solution was used to clot the thrombin formed by the interaction of serozyme, calcium and cytozyme, the clots required a slightly longer time to form than if normal fibrinogen was used. This was probably due to the fact that the normal plasma contained a few platelets which acted to accelerate the reaction more than the very few hemophilic platelets in their plasma.

STUDIES ON THE WHOLE BLOOD

Addition of Platelets to Whole Blood.—Blood was drawn from the arm vein of a hemophilic patient and 1 c.c. put in each of a series of tubes. One c.c. of this blood coagulated in fifty-five minutes. The addition of one drop of a weak suspension of fresh normal platelets caused this blood to clot in fifteen minutes, while two drops of a correspondingly weak suspension of hemophilic platelets caused the blood

TABLE 8.—COAGULATION TIMES OF WHOLE BLOOD, THE PROTHROMBIN TIME, AND ANTITHROMBIN FACTOR; THE EFFECT OF TRANSFUSION ON THE COAGULATION TIME

Date	Coagulation Time, Min.	Prothrombin Time, Min.	Prothrombin Control, Min.	Anti-thrombin Factor	Remarks
Case 1					
March 10.....	55	No bleeding or change in patient's condition
March 13.....	70	50	10	1+	
March 19.....	40	28	8	1.5	
March 23.....	70	50	8	1.35	
March 26.....	50	45	10	1.2	
Case 2					
March 19.....	100	70	8	1.35	No change in patient's condition or bleeding
March 21.....	60	40	12	1.3	
March 23.....	92	60	10	1.15	
March 31 (before transfusion)	150	85	12	
March 31 (after transfusion)	8	
March 31 (6 hours after transfusion)	10	March 31 transfused 600 c.c. of blood from donor, whose coagulation time was 7
April 1.....	17	April 7 spontaneous hemorrhage into right knee joint
April 2.....	25	
April 3.....	60	
April 5.....	100	
April 12.....	55	
April 14.....	115	
April 20.....	100	

to coagulate in forty minutes. One drop of a "saturated" suspension of normal platelets caused coagulation in five minutes and double this amount of hemophilic platelets caused coagulation in twenty-five minutes. The first fibrin strands in the tubes containing the hemophilic platelets appeared from one to four minutes after they appeared in those with the normal platelets, but coagulation proceeded to completion much more slowly. It is important in order to get these wide differences to use fresh preparations of platelets. We have found that

the hemophilic platelets on standing for over twenty-four hours seem to undergo some change, since in some instances these old hemophilic platelets acted more rapidly than the freshly prepared platelets. The results with hemophilic and normal bloods were consistent with those obtained with the hemophilic plasma, oxalated hemophilic, and normal blood plasma.

Studies on the Coagulation Time of the Whole Blood.—The coagulation time of the whole blood was determined by the method of Lee and White,¹⁹ which is to allow 1 c.c. of blood drawn from a vein to clot firmly in a tube eight mm. in diameter. By this procedure normal blood clots in five to ten minutes. The results are seen in Table 8, and show the usual prolongation of the coagulation time of hemophilic blood. Fluctuations occurred without evident reason, such as has been noted by others.

CASE 1.—A man, 50 years of age, and the man in Case 2, who was 25 years of age, both gave a clean cut family history of hemophilia and had suffered from nose bleeds and severe bleeding from injuries. One gave a history of hematuria. Both had suffered since childhood with repeated attacks of swelling, stiffness and pain in the various joints of the body and the joints gave the typical appearance of chronic hemophilic joints. In Case 1 there had been no acute joint swelling or pain for three months before entrance, but the patient had had some bleeding from his gums six weeks previously, associated with carious teeth. In Case 2 there was an acute swelling of the knee some two months before entrance, but the patient had had no other hemorrhagic symptoms for over a year. During his stay in the hospital he developed again acute swelling and pain in his knee, subsiding after ten days. Otherwise during the present study of these cases there was no evidence of bleeding.

CASE 2 is of especial interest. In view of the fact that normal platelets in small amounts in vitro could shorten the hemophilic coagulation time, it was thought that the transfusion of normal blood might shorten the coagulation time of the hemophilic blood, and that the lasting effect of such a procedure would be evident as long as the life of the normal transfused platelets. To test this point, with the enthusiastic approval of the patient Dr. Vincent transfused the second patient with 600 c.c. of blood from a donor of the same iso-agglutination group, whose coagulation time was seven minutes and whose platelets were normal in numbers. Before the transfusion 500 c.c. of blood were removed from the patient. Allowing that the patient's and donor's blood volume was 5 liters, the number of normal platelets that were given this patient would be about 24,000 per c.c.

The coagulation time one and one-half hours before transfusion was 150 minutes. On this same day directly before transfusion the coagulation time determined by obtaining blood through a paraffined cannula and allowing it to run directly into the glass coagulation time tube was four and one-half hours. It was quite striking to find directly after the transfusion that the hemophilic blood clotted in normal time, as it also did six hours after transfusion. There was a definite gradual lengthening of the coagulation time, so that it was sixty minutes three days, and 100 minutes five days, after the transfusion.

Thus the effect of the transfusion was not evident after three days. This time coincides with our ideas of the life of the platelets, as pointed

19. Lee and White: Am. Jour. Med. Sc. 1913, cxlv, 495.

out by Duke.²⁰ It seems reasonable to suppose that the effect of the transfusion was due to the normal platelets, that as they began to "die" the coagulation time lengthened and kept on doing so until its previous delayed time was reached, at which time all the normal platelets had died off.

Character of the Blood Clot.—The clots of the whole blood always retracted fully as much as normal clots and gave the typical appearance of hemophilic clots, that is, white on top, red below, with greater retraction at the top of the clot because of the richness of the platelets in this region. Clots from clear plasma did not retract unless a sufficient amount of platelets had been added; these clots never seemed to retract as well as blood or cloudy plasma, containing numerous platelets which had not been first removed.

If after the hemophilic blood had apparently clotted firmly the clot was loosened and removed from the fluid, the fluid would clot and would do so sometimes almost at once, often in three to five minutes and sometimes not for ten to thirty minutes or more. Again on separating the clot, but not removing it from the serum, this reclothing phenomenon occurred and might be repeated from three to six times. The reclothing would occur no matter whether the clot was loosened a few minutes or a few hours after it had appeared solid. If one waited hours rather than minutes after the clot had formed, one usually obtained the reclothing phenomenon fewer times. This same phenomenon was observed on clotting hemophilic oxalated plasma with calcium to obtain serozyme. (It was first called to our attention by Dr. Howell.) This phenomenon has been observed in a number of cases of hemophilia and in other cases with delayed coagulation time and prolonged prothrombin time. Of some twenty-five observations on eight cases which have exhibited this phenomenon, none have shown an antithrombin content below one,²¹ while almost all the observations have shown an increase in antithrombin. It was thought, as suggested by Dr. Howell, that the increased antithrombin content had something to do with this phenomenon. This phenomenon is also seen in preparing serozyme from very clear normal oxalated plasma. An explanation which now occurs to us is that the phenomenon is associated with a slow formation of thrombin. Thrombin may be slowly formed from at least two causes traceable to blood platelets. In the case of hemophilia the blood platelets, while sufficiently numerous, are not readily available for purposes of coagulation, hence a slow formation of an ample amount of thrombin. In the case of purpura hemorrhagica associated with a low blood platelet count we may have a slow formation due to the paucity of blood platelets. Under normal conditions

20. Duke: Jour. Exper. Med., 1911, xiv, 265.

21. Minot, Denny and Davis: THE ARCHIVES INT. MED., 1916, xvii, 101.

there is probably an excess of blood platelets, and as several observers have elsewhere shown, the excess of blood platelets over the number actually required for coagulation acts in retracting the clot. In purpura hemorrhagica there is no clot retraction, since all the blood platelets are used for thrombin formation, which is relatively slow due to the necessity of using all the blood platelets.

FURTHER STUDIES ON PLATELETS

In these two cases of hemophilia the platelet count determined by Wright and Kinnicutt's²² method was from 290,000 to 400,000, that is at or slightly above the upper limit of normal.

The Bleeding Time.—The time a patient bleeds from a puncture in the ear has been shown by Duke²³ to be prolonged in conditions with very few platelets. In such conditions, however, the coagulation time is often normal, although it may be somewhat delayed. It seems that in such cases there is enough thrombin to allow the blood to clot in normal time, or not greatly beyond the normal time, though in our experience a weak clot occurs. One must realize that it probably takes very few normal platelets to do their share in allowing blood to coagulate in normal time and that a little thrombin can cause fibrinogen to clot, though weakly, in the same time as much larger amounts; while with minimal amounts of thrombin the time is delayed and the clot is weak. Duke tested the bleeding time of but one case of hemophilia and found it normal. Other observations have recently been made by Hess,⁷ who found this time normal in several hemophilic cases, which is in accord with our repeated findings in these two cases and also in three others of typical hemophilia. The bleeding time from an arm vein was also normal in these cases. It is rather surprising that typical cases of hemophilia, in which bleeding occurs readily after cuts, injuries, etc., and which show a marked delay in the coagulation time of the blood, do not always have an abnormal bleeding time. Whether this is to be considered entirely due to the fact that their platelets are plentiful in numbers will be referred to later.

Studies on the Metamorphosis of the Platelets.—Under the microscope we have repeatedly observed the agglutination and fusion into glassy-like masses and often dissolution of the platelets that occurs when any serum containing active thrombin and calcium is allowed to act on platelets. The action of antithrombin, oxalated plasma, pure thrombin, etc., and combinations of such blood elements on blood platelets is reserved for a future communication. We were, however, unable to detect that hemophilic or normal serum, antithrombin, sero-zyme, plasma, pure thrombin and calcium and various combinations of

22. Wright and Kinnicutt: Jour. Am. Med. Assn., 1911, lvi, 1457.

23. Duke: THE ARCHIVES INT. MED., 1912, x, 445.

such substances acted differently on hemophilic than on normal platelets. No matter whether the platelets were washed one or more times or whether they were obtained from oxalated plasma or magnesium sulphate plasma. Whatever permitted the metamorphosis of the hemophilic or normal platelets did so as readily and quickly with hemophilic as with normal coagulation elements. Dr. J. Homer Wright could find no particular histologic difference in the fused masses of hemophilic and normal platelets, whether caused by hemophilic or normal serum acting on the platelets for a longer or shorter period.

It is noteworthy that no fusion or microscopic change occurred in the platelets in the hemophilic plasma or blood until fibrin strands began to form from thirty to forty minutes after withdrawing the blood, which clotted firmly in seventy minutes. Practically all the platelets were more or less fused, some more than others, five to eight minutes after the process began.

The platelets from the depth of the red cell sediment obtained after centrifugalizing twenty minutes the whole blood and after the plasma was removed appeared clumped, but not fused. After some hours these platelets appeared the same, though the plasma had clotted. After twenty-four hours they appeared disintegrated, rather than fused, and the red cell sediment showed no clot.

It has often been suggested that the platelets are important factors in the coagulation of the blood and that they have something to do with the initial stage of coagulation. In most theories it is agreed that immediately as blood is shed it undergoes some change which makes it quite different from normal circulating blood and enables coagulation to ensue. The duration of this stage is probably short, but concerning it very little is known. It is perhaps significant that with the first visible signs of coagulation the platelets begin to undergo this metamorphosis. Perhaps before coagulation and metamorphosis of the platelets can properly proceed, certain substances in the platelets must go into solution. Such substances derived from the platelets probably occur in solution in the circulating blood.

ULTIMATE FATE OF THE BLOOD PLATELETS

It has been shown by Wright²⁴ that the platelets are formed from the megakaryocytes of the bone marrow and spleen. Their life is short, probably a few days, as shown by Duke and as suggested by the results of transfusion in our hemophilic patient. The ultimate destiny of the blood platelets has not been studied. We have no knowledge on this point. There must be a constant destruction. A possible explanation is that after their disappearance as fixed elements in the blood the active principle presumably is taken up by the tissues and is present in

24. Wright: *Jour. Morphology*, 1910, xxi, 263.

tissue juice and known as the thromboplastic substance of the fixed tissues. The active coagulating principle of tissue juice accelerates coagulation in a similar fashion as do the blood platelets. If this theory is correct and if we may assume that the difficulty with hemophilic platelets is that they cannot go into solution or start to make thrombin as readily as normal platelets, one ought to be able to show two things: first, that hemophilic tissue juice acts as efficiently as normal; secondly, that hemophilic platelets in solution are more effective than in suspension, that is, in solution their action is like normal platelets in suspension.

Sahli⁹ and Morawitz and Lossen⁸ have believed that the hemophilic tissue juice was lacking in thromboplastic activity, but they have given no experimental proof. Gressot²⁵ is the only one who has studied the thromboplastic action of hemophilic tissue. He showed from a study of hemophilic organs obtained at necropsy that the tissue juice of hemophiliacs is as active as normal. One of us had the opportunity one and one-half years ago to study the thromboplastic activity of hemophilic tissues obtained from a patient with typical hemophilia, who died after having transfusion performed. We found, as did Gressot, that we could not detect any ineffectiveness of the hemophilic tissue to accelerate the coagulation of normal blood or normal recalcified oxalated plasma, but its action on hemophilic blood or plasma was not tested. However, the hemophilic tissue acted in no wise differently from normal tissue juice.

On the theory that platelets on being destroyed go into solution and this substance in solution is what is known as tissue juice we might explain the reason for a normal bleeding time in hemophilia in the following manner: Once that the resistant hemophilic platelets go into solution we have an essentially normal tissue juice. It is the tissue juice that is the important element that affects the bleeding time, rather than the number of platelets. The thromboplastic substance appears to be normal in hemophilic tissue and perhaps when a small puncture is made in the ear to test the bleeding time enough of the tissue juice exudes to allow the blood to clot rapidly. If the wound is large so that loss of blood is comparatively rapid and great, we can conceive that enough tissue juice is not available to check such a hemorrhage occurring with a blood with such an abnormal coagulation time. We have occasionally observed that with a grossly faulty technic of vein puncture which allowed a liberal addition of tissue juice, that the hemophilic blood clotted in time approaching that of normal blood and that the hemophilic plasma from such a blood approached normal plasma in its behavior. On the contrary, in cases of purpura hemorrhagica with a diminished number of platelets and

25. Gressot: Footnote 1, third reference.

an abnormally long bleeding time, it is possible to explain the long bleeding time by supposing that it is due to a deficiency of the tissue juice, which in turn is conceivably dependent on a constant replenishment from the solution of the platelets in the tissues, rather than that the bleeding time is entirely dependent on the number of platelets. On such a hypothesis the few platelets would be the cause of the diminished amount of tissue juice and this diminished quantity of active tissue juice would be more directly the cause of the prolonged bleeding time than the few platelets per se.

We have no evidence that tissue juice of cases of purpura hemorrhagica is or is not normal. The observation of Minot²⁶ on the thromboplastic activity of the uterus removed at operation in such a case is perhaps at first sight against such a theory. He observed that this tissue had thromboplastic activity. On this patient, however, transfusion had been performed forty-eight hours before and also directly before the operation, which might well have altered the thromboplastic content of the organ. Again, differences of thromboplastic activity might be less capable of demonstration on normal plasma than on hemophilic. This was not done.

In regard to the solution of the platelets, we investigated the relative fragility of hemophilic and normal platelets and the efficacy of so-called platelet solutions in accelerating coagulation as contrasted with platelet suspensions. Attempts were made to test the fragility of normal and hemophilic platelets against varying strengths of salt solution, as one tests the fragility of the red cells. No differences could be detected, macroscopically, in regard to their solution. This was because normal platelets even in distilled water do not break up as do red cells. They swell and change their morphologic character somewhat, but to the naked eye the mass left after standing several hours in either normal salt solution or water appears the same. However, if the supernatant fluid is removed from the platelets which have been in water for some time and compared to salt solution in which platelets have stood, the water solution clearly has more thromboplastic action than the salt. Further studies on the microscopic appearance of the platelets after standing in different strengths of salt solution are desirable.

Hemophilic platelet solutions and suspensions were made numerous times and tested to see if we could find any difference in their cytolytic action. It was found impossible by simply using water to get complete solution, so that our platelet solutions always contained some platelets in suspension. The protocol in Table 7 shows the results obtained several times when hemophilic platelet suspensions and extracts were added to hemophilic clear plasma.

26. Minot: *Am. Jour. Med. Sc.*, 1916, clii, 48.

In these experiments it did seem as if the hemophilic platelet solution was more efficient than the hemophilic platelet suspension in its ability to clot the hemophilic plasma. If the solution was kept an hour or so before it was used it was sometimes, but not always, more effective than if used directly after it was made up.

One series of experiments was made with extracts and suspensions of normal and hemophilic platelets on accelerating the clotting time of recalcified hemophilic oxalated plasma. Differences between the action of extracts and suspension were very slight. After both acted equally well and such differences as shown when the plasma was studied were not demonstrated.

Attempts were also made to see if extracts of normal and hemophilic platelets were more effective in forming thrombin with serozyme and dilute calcium than suspensions of normal and hemophilic platelets. The results varied. Perhaps more frequently the extracts seemed to be rather better than the suspensions in being able to form thrombin. On the other hand, the reverse result was sometimes obtained. We have at present no satisfactory explanation for the inconsistent results of these experiments.

From the results of our studies on the ability of platelets in solution to act more efficiently than in suspension, it is seen that one set of experiments showed this to be apparently true, while other experiments were inconclusive or negative. It is desirable to study such differences probably by other means, by aid of other substances to cause better solutions, for example, action of minimal doses of roentgen rays, etc. At present one can say that some results are suggestive of differences. This is not entirely in accord with Fonio,²⁷ who found solutions of platelets less or equally active with their suspensions.

THE PROTHROMBIN TIME

The prothrombin time, the time it takes a solid clot to form from oxalated plasma on recalcification with the optimum amount of calcium, was determined by the method described by Howell⁵ and discussed by Minot,²⁸ and by Minot, Denny and Davis.²¹ This time was found abnormally long, as may be seen by referring to Table 8. Such a markedly delayed prothrombin time is characteristic of hemophilic blood, as has been shown by Howell,⁵ Addis,¹³ Hurwitz and Lucas,⁶ Minot, Denny and Davis,²⁴ and Hess.⁷ There was no evidence that the available calcium was at fault in these hemophilic cases, as evidenced by the fact that the optimum amount of calcium needed to recalcify the plasma from the cases and the controls was the same. The *in vitro* test

27. Fonio: Footnote 1, first reference.

28. Minot: *Jour. Med. Research*, 1916, xxxiii, 503.

of Lee and Vincent²⁹ showed that a drop of calcium added to 1 c.c. of blood or plasma did not alter the coagulation time or shortened it but very slightly, not giving the striking changes seen in certain cases of jaundice.

THE ANTITHROMBIN

The antithrombin was tested for by a modification of Howell's⁵ method and that previously used by Minot, Denny and Davis.²¹ This modified method gives less variation of the antithrombin in normal blood than that previously found by Minot, Denny and Davis. The antithrombin factor or quotient was found to be normal or more usually slightly above normal (Table 8). Such findings have been reported before. It is unfortunate that we were unable to determine the prothrombin time and antithrombin in the second case after transfusion. A heavy suspension of hemophilic platelets was able to neutralize antithrombin from hemophilic serozymes, plasma or serum as rapidly and readily as normal platelets. Dealing with dilute suspensions of platelets, which are notoriously uncertain in regard to their equality, we seemed to find the hemophilic platelets less able to neutralize antithrombin than were normal platelets.

MISCELLANEOUS STUDIES

The addition of normal or hemophilic active serozyme to whole hemophilic blood or normal or hemophilic recalcified oxalated plasma did not affect the clotting time if the serozyme was free of thrombin.

The addition of an amount of pure thrombin made according to Howell's³⁰ methods fully sufficient to clot solidly normal blood or oxalated plasma in two minutes likewise clotted solidly in two minutes hemophilic blood, plasma or oxalated plasma. When an amount of pure thrombin was used that just clotted firmly normal plasma the hemophilic plasma might be clotted a little less firmly. Such differences as this in these cases were very slight. In the study of various cases in the past, though not without exception, such a difference has been concomitant with an increase of antithrombin, as it was in these cases.

The addition of cephalin, or tissue extracts, like normal platelets, clotted hemophilic plasma or blood rapidly.

Hemophilic serum clotted normal or hemophilic plasma equally well and in essentially the same time as did normal serum.

We have tested the hydrogen ion concentration of the blood in these cases by the method described by Levy, Rowntree and Marriott³¹ and found it normal, as did Hurwitz and Lucas.⁶

29. Lee and Vincent: *THE ARCHIVES INT. MED.*, 1915, xvi, 59.

30. Howell: *Am. Jour. Physiol.*, 1910, xxvi, 453; *ibid.*, 1913, xxxii, 264.

31. Levy, Rowntree and Marriott: *THE ARCHIVES INT. MED.*, 1915, xvi, 389.

We have found no evidence in several cases of hemophilia of any fibrinolytic ferment present in the circulating blood during life. This is in accord with Morawitz and Lossen⁸ and the recent findings of Hurwitz and Lucas.⁶

Dr. A. H. Rowe tested the albumin and globulin content of the plasma by T. B. Robertson's methods and found it essentially normal as did Hurwitz and Lucas.⁶

In regard to the occurrence of nontypical types of hemophilia, we would like to emphasize that there are various atypical and intermediate types of hemophilia and purpura hemorrhagica; that there is undoubtedly a hereditary type of purpura and that this may occur in a female member of a family, some of whose male members are typical hemophiliacs; that atypical cases giving a history of hemophilia may at certain times have a normal or nearly normal coagulation time; that an antithrombin increase may perhaps at times be more marked than normal in some of these cases; that some cases may appear at one time to be more of a hemophilic nature and at other times more of a purpuric nature; that is, at one time they may show a normal platelet count, but a marked delay of the coagulation time, while at other times the coagulation time may be less delayed, while the blood platelets are very few in numbers.

The fact that cases of purpura hemorrhagica are associated with few platelets, on which the bleeding time depends indirectly or directly, and that cases of intermediate types of purpura and hemophilia exists, suggests again that an alteration in the platelets is the cause of the abnormal coagulation phenomenon of hemophilic blood. We would suggest from our studies that the hemophilic platelets are qualitatively defective in that they cannot start the process of coagulation as well as normal platelets, that as cytozyme they cannot act as rapidly to form thrombin or to accelerate the coagulation of the blood. In Howell's terminology we can interpret our findings to indicate that the hemophilic platelets cannot give up their prothrombin so readily as normal platelets, rather than that they are deficient in their prothrombin content; this would agree with Addis' conception of the cause of the slow coagulation of hemophilic blood. If this is true, one would expect to find a marked diminution compared to normal in the circulating prothrombin in solution, while the total prothrombin (in solution and bound) would occur in normal amounts. Perhaps the much delayed prothrombin time of hemophilic plasma is explained on such a basis, that is, that it contains minimal amounts of free soluble prothrombin or its antecedents.

SUMMARY AND CONCLUSIONS

The blood platelets from two typical cases of hemophilia have been studied, because in the course of some work on coagulation we have been greatly impressed by the importance of the blood platelets. Previous work has shown that in typical hemophilia the formed elements are in essentially normal numbers. The calcium and fibrinogen content of the blood and thrombin in the serum are within normal limits. The antithrombin is normal or often slightly increased. The activity of the tissue juice is probably normal. The prothrombin time is markedly delayed. These results agree with the findings in our cases.

The hemophilic blood platelets were obtained directly from the blood and from various types of salted plasmas. If normal blood platelets in about normal amounts were added to hemophilic plasma they caused it to coagulate in a time that is normal or nearly normal. When hemophilic blood platelets were added even in approximately seventy-five times as great a concentration as in normal blood, though they definitely shortened the coagulation time, they never brought that time to anything approaching normal limits.

By using the method of formation of thrombin described by Bordet and Delange, the blood platelets required more time to form thrombin when derived from hemophilic than from normal blood. This is consistent with the reclothing phenomenon observed in hemophilic bloods.

Microscopically, under favorable conditions of thrombin, etc., hemophilic platelets undergo the usual transformation in apparently normal time. Under the most favorable conditions hemophilic platelets act nearly normally. On the other hand, in the case of oxalated plasma, recalcified by an amount of calcium that is not the optimum amount, wide discrepancies are seen in the clotting times when normal and hemophilic platelets are added.

This evidence suggests, as does the fact that partial solution of the hemophilic platelets in water was usually more efficient than hemophilic platelets in suspension, that the delay in coagulation in hemophilia occurs in the initial step in coagulation, which seems to be a rendering of the platelets available by some process like solution.

We are inclined to present the theory that the active coagulating principle of the tissue juice is derived in part, if not wholly, from the blood platelets. As evidence on this point we present the fact that in hemophilia with a normal number of abnormally resistant platelets we have a very abnormal coagulation time, but a normal bleeding time. In purpura hemorrhagica these conditions are just the opposite. The normal number of platelets, though few in number, are sufficient to form a little thrombin and clot fibrinogen in essentially normal time. The value of an excess of platelets seems to be to furnish the active coagulating principle of the tissue juice.

On one of the hemophilic patients transfusion was performed with 600 c.c. of normal blood. The coagulation time before transfusion was from sixty to 120 minutes. After transfusion it was seven minutes. A gradual lengthening of the coagulation time occurred for three days, when it was again sixty minutes. Since about three days is generally assumed to be the length of life of the blood platelet, our actual clinical findings seem to corroborate the findings in vitro.

We conclude that in hemophilia we have an hereditary defect in the blood platelets. This defect consists of a slow availability of the platelets for the purposes of coagulation.

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THE EXCRETION OF CHLORIDS AND WATER AND THE RENAL FUNCTION IN SERUM DISEASE *

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AND

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Since the classical work of von Pirquet and Schick on serum disease, it has been repeatedly observed that with the edema which appears in the course of this illness, albumin and occasionally casts may occur in the urine, and a few observers have noted suppression of urine with subsequent albuminuria and cylindruria during severe immediate or accelerated reactions following a second dose of serum. Though these symptoms are said to be transient, no accurate studies have so far been made to determine whether actual changes take place at this time in the functional activity of the kidneys, and since it has been shown by one of us¹ that repeated injections of foreign protein in sensitized animals may lead to damage of the kidney, as well as to the other organs, it seemed important to determine whether the edema, which is often general in serum disease, is associated with any transient impairment of the kidney function.

For this purpose ten cases of serum disease have been studied. Most of the patients were young adults, five below the age of 25; of the remainder, one was 29, one 31, one 36, one 48 and one 49. None of them gave a history which would suggest any previous disease of the cardiovascular system or of the kidneys and none presented any signs of chronic diseases when they entered the hospital. In nine patients serum disease followed the intravenous use of antipneumococcus serum and in one the intraspinal injection of antimeningococcus serum.

The methods employed to study the functional activity of the kidneys have been as follows: Immediately after the patient received the first therapeutic injection of serum, which in every instance was horse serum, he was given a suitable diet that contained as nearly as possible a constant quantity of sodium chlorid. This varied in different instances, but during the period of the disease in which the diet contained fluid or only eggs, bread and cereals, the patient received from 2 to 3 gm. of salt a day; later when the diet was increased the amount of sodium chlorid varied from 6 to 10 gm. a day. The total fluid intake was fixed at 2,500 c.c. or 3,000 c.c., according to the needs of the

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1. Longcope: Jour. Exper. Med., 1913, xviii, 678.

person. On this constant intake of sodium chlorid and fluid the daily output of urine was measured and the chlorid estimated by the Mohr method. In a few instances the chlorids of the plasma have been determined by the McLean and Van Slyke modification of Volhard's² method, at various intervals, before, during and after the serum sickness. In the same way the total blood urea has been estimated by the urease method and the index of urea excretion studied according to McLean's modification³ of the Ambard formula. Together with these procedures the excretion of phenolsulphonephthalein has been tested at intervals during the course of the disease.

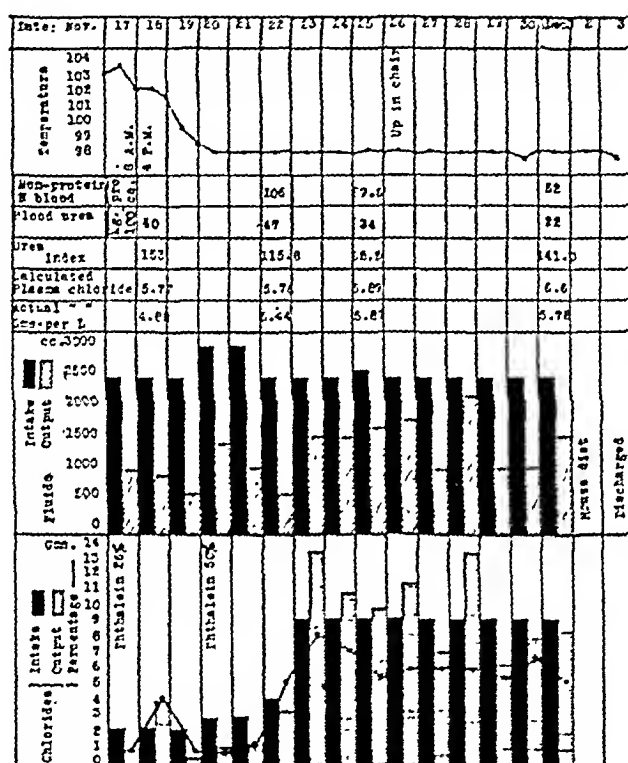


Fig. 1.—M. S., man, aged 34, with lobar pneumonia, pneumococcus Type 1. The usual course of water and chlorid excretion, the changes in nonprotein nitrogen, urea and chlorids of the blood and phenolsulphonephthalein excretion during convalescence from uncomplicated lobar pneumonia.

As most of the cases of serum sickness occurred during convalescence from pneumonia and since it is known that the excretion of chlorid as well as the nitrogenous metabolism is greatly disturbed in this disease, it was necessary to apply, as a control, the same methods of study to several convalescing pneumonia patients who had not received serum. Five such patients were followed during their convalescence. During the attack of pneumonia, as is well recognized, the excretion of chlorid is greatly diminished. The plasma chlorids fall

2. Jour. Biol. Chem., 1915, xxi, 361.

3. Jour. Exper. Med., 1915, xxii, 212.

below normal and the amount of urine is small. Three to four days after the crisis the plasma chlorids rapidly rise and the excretion of chlorids increases so that the chlorids retained during the disease are eliminated within a few days. During this time they are excreted in excess of the intake and in high concentration. Very rapidly, however, a balance is established and the normal ratio of excretion is reached.⁴

The curves shown in Figure 1 show the characteristic changes in water and salt excretion of the five cases studied as controls.

During the convalescence from pneumonia there may be a disturbance in nitrogenous metabolism, the total blood urea varying considerably from the normal figure. For this reason no deduction can be drawn from the estimations of urea and the nonprotein nitrogen of the blood in the cases of serum disease. The index of urea excretion, however, remained unaltered in three of the control cases. Table 1 gives the determination of phenolsulphonaphthalein for a two-hour period, of the blood urea, the urea index and the plasma chlorids in four control cases. In Cases 1 and 4 these estimations were made both before and after the crisis.

TABLE 1.—PHENOLSULFONEPHTHALEIN EXCRETION, BLOOD UREA AND INDEX OF UREA EXCRETION AND PLASMA CHLORIDS IN CASES OF UNCOMPLICATED LOBAR PNEUMONIA

Control Cases Uncomplicated Pneumonia	Date	Phenolsul- phone- phthalein, per Cent.	Blood Urea, Mg. per 100 c.c.	Urea Index	Plasma Chlorids, Gm. per Liter	Remarks
1	10/18	26	40	153	4.88	Before crisis
	10/20	50	Before crisis
	10/22	..	47	115.8	5.44	After crisis
	10/25	..	34	68.5	5.87	After crisis
	12/ 1	..	22	141	5.78	After crisis
2	1/14	64	16	171	5.5	After crisis
3	1/ 4	46	At crisis
4	11/17	56	Before crisis
	11/30	51	After crisis
	12/ 1	..	32	113	5.52	After crisis

As compared with these controls a study of the ten cases of serum sickness showed that during this illness the excretion of phenolsulphonaphthalein and urea was little affected. Table 2 gives the estimation of phenolsulphonaphthalein for a two-hour period, the blood urea and index of urea excretion in the ten cases. In Case 3 the excretion of phenolsulphonaphthalein has slightly diminished, in Case 4 at the

4. Peabody: Jour. Exper. Med., 1913, xvii, 71. McLean: Ibid., 1915, xxii, 366.

onset of serum sickness the phenolsulphonephthalein excretion was far below normal and the blood urea distinctly elevated. Unfortunately the index of excretion was not determined, but before recovery from serum disease the blood urea had fallen to the normal level. In Case 9 the blood urea was also high, but the index normal. In Case 10 there was a transient but marked reduction in excretion of phenolsulphonephthalein during the serum sickness.

Much more profound changes were observed, however, in the excretion of water and chlorids than in the excretion of nitrogen and

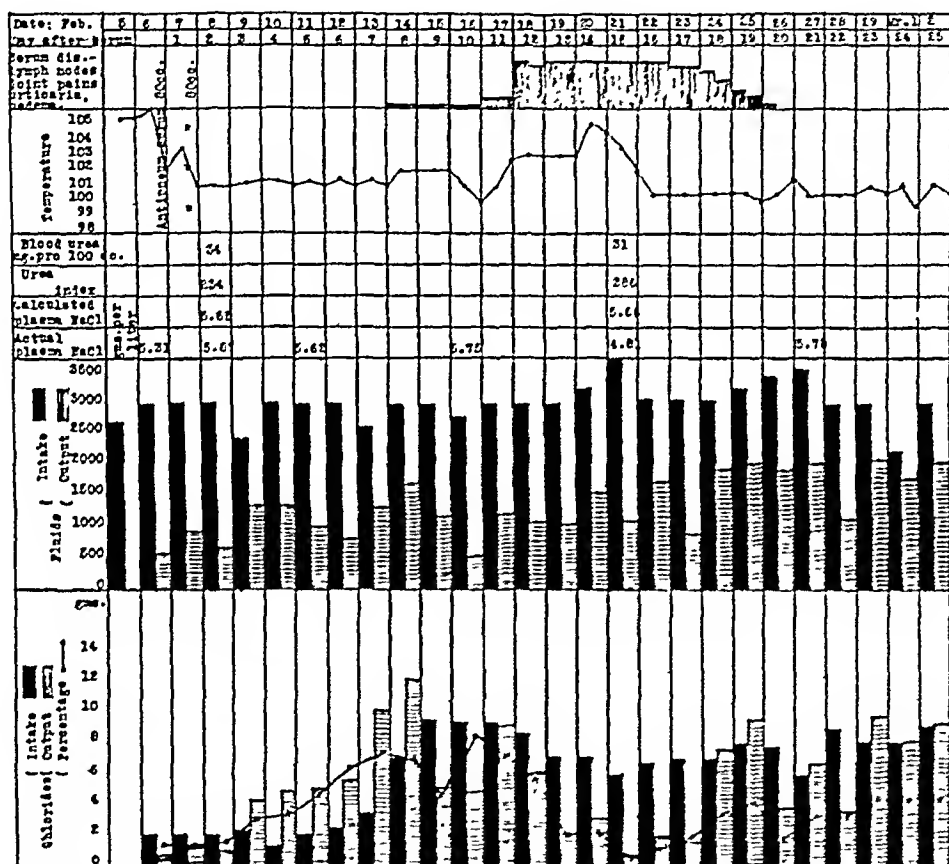


Fig. 2 (Case 5).—W. B., man, aged 31, with lobar pneumonia, pneumococcus Type 1, with serum disease following the intravenous injection of serum. The course of water and chlorid excretion, the changes in blood urea, urea index, plasma chlorids, and excretion of phenolsulphonephthalein during convalescence from pneumonia complicated by serum disease. The severity of the serum disease is indicated by the height of the block in that section.

phenolsulphonephthalein. This was observed in eight of the ten cases. The two cases that did not show any deviation from the controls were Cases 1 and 2.

In Case 1 the patient received two doses of 90 c.c. of antipneumococcus serum intravenously, which was followed in eight days by mild urticaria lasting forty-eight hours, while in Case 2 the administration of the same amount of serum intravenously was followed in eight days by a fairly severe urticaria of four days' duration.

TABLE 2.—PHENOLSULPHONEPHTHALEIN EXCRETION, BLOOD UREA AND INDEX OF UREA EXCRETION AND PLASMA CHLORIDS BEFORE, DURING AND FOLLOWING SERUM DISEASE

Case No.	Before Serum Disease				During Serum Disease				After Serum Disease			
	Phenol-sulphone-phthalein, per Cent.	Blood Urea, Mg.	Urea Index	Plasma Chlorids	Phenol-sulphone-phthalein, per Cent.	Blood Urea, Mg.	Urea Index	Plasma Chlorids	Phenol-sulphone-phthalein, per Cent.	Blood Urea, Mg.	Urea Index	Plasma Chlorids
1	48	32	480	...	58	24* 21	251 410	22 18	436 466
2	31 32	26
3	30 59	45 36	54	28
4	45 33 47	60
5	16.4 48 20 45	110 34 20 20
6	75	34	234	5.31 5.87 5.62 5.75	64	31	386	4.81	5.78
7	80 ..	24 31
8	54	16	300	6.125	53	11	148	6.50	62	10	235	6.50
9	..	39	50 62 ..	33 20 16
10	55	68 ..	46 65	120 151	...	64 74	12 24	163 133.75
	50	40	111	...	18	20	113	...	65

* When two or more figures occur in the same column for a single case, they represent separate estimations at from two to four days interval.

The remaining eight cases fall into two distinct groups. In the first, which comprises six cases (Cases 3, 4, 5, 6, 8 and 9) the following changes were observed: At the onset of serum sickness the excretion of chlorids fell to a low figure, so that on an intake of 5 gm. of sodium chlorid, less than 1 gm. was eliminated. At the same time the total volume of urine diminished so that the chlorids were excreted in very low concentration. During this time the addition of 10 extra grams of sodium chlorid to the diet in Cases 4 and 8 (Fig. 3) caused no increase in excretion of chlorids in the urine. With recovery from the symptoms of serum sickness the chlorids were eliminated greatly in excess

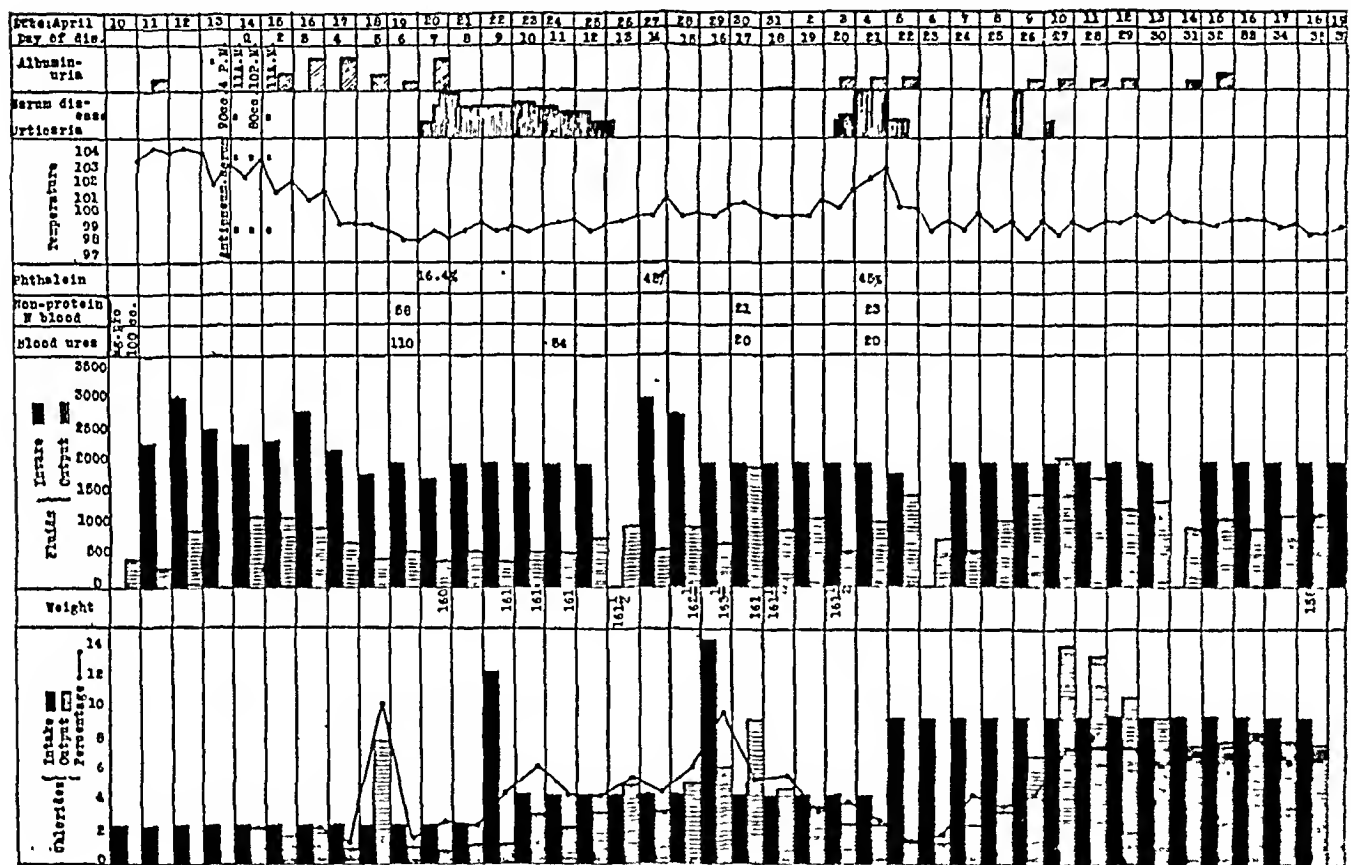


Fig. 3 (Case 4).—M. H., woman, aged 49, with lobar pneumonia, pneumococcus Type 1, with serum disease following the intravenous injection of serum. The course of water and chlorid excretion, the changes in the nonprotein nitrogen of the blood, blood urea, and excretion of phenolsulphonephthalein, in convalescence from pneumonia complicated by severe and relapsing serum disease. The severity of the serum sickness is represented by the height of the blocks in that section.

of the intake, in moderately high concentration, and were often associated with a mild diuresis. One patient, Case 8, who on an average intake of 4.5 gm. of sodium chlorid had been retaining chlorids during a prolonged attack of serum disease lasting twenty-two days, eliminated after recovery 12 to 16 gm. of chlorids on a daily intake of 6 gm. of sodium chlorid, while the daily output of urine on an intake of 2,500 c.c. of fluid suddenly increased about 1,000 c.c.

The degree of water and chlorid retention seems to depend on the intensity of the serum disease, rather than on the amount of serum given, for the disturbances were quite as marked in one boy of 15 who received two doses of 40 c.c. of antipneumococcus serum intraspinally as in a man of 31 who received a total of 160 c.c. of serum intravenously.

Figures 2 and 3, from Cases 5 and 4, illustrate well the type of alteration observed. In Case 5 (Fig. 2), that of a man of 31, the critical close of his pneumonia was followed by the usual excessive excretion of chlorids in high concentration. With the onset of serum disease the daily elimination of chlorid immediately fell from 1 to 3 gm. a day on an intake of from 6 to 7 gm., and the percentage was reduced below 0.2. With recovery from serum disease the retained chlorids were again excreted and the quantity of urine increased.

In Case 4 (Fig. 3) the injection of 240 c.c. of serum in four doses resulted in a severe and relapsing type of serum disease lasting twenty days. It will be seen from Figure 3 that the additional 10 gm. of salt in the diet on the third day of the serum disease was not excreted and that the same procedure during the intermission between the two severe attacks of serum disease was followed by a very slight response, as evidenced by the moderate increase in the excretion of chlorid during the next forty-eight hours.

The question immediately arises as to whether the chlorids in these cases are retained in the tissues or in the blood. McLean has reported a case of serum disease after pneumonia in which the retention of chlorids was associated with a high plasma chlorid. A study of the plasma chlorids in this group seemed to indicate that the chlorids are retained in the tissues rather than in the blood. In one case (Case 5) the plasma chlorids were carefully followed before, during and after the serum sickness. The results are shown in Table 2 and in Figure 2. Immediately before the crisis the plasma chlorids were somewhat lower than is generally conceded to be the normal figure for the threshold of excretion, which is put at 5.62 gm. per liter. At this time the plasma chlorids were 5.31 gm. per liter. Immediately after the crisis they rose to 5.87 gm. per liter; three days later they were 5.62 gm. per liter. The day before serum disease appeared they were 5.75 gm. On February 21, the fourth day of the serum disease, they had fallen to the extremely low figure of 4.81 gm., while on February 27, two days after recovery from serum sickness, the plasma chlorids had risen to 5.78 gm. and chlorids were being excreted in large quantities in the urine.

We may therefore conclude that in this group of cases the marked retention of water and chlorids takes place in the tissues and is associated regularly with albuminuria of mild degree, with the presence of

casts in the urine and occasionally (Cases 3 and 4) with a transient disturbance in the excretion of phenolsulphonphthalein.

In the second group, which comprises only two cases, 7 and 10, the excretion of salt and water is affected in a different manner. Both of these patients were women, one 48 years of age, the other 29 years old. One patient (Case 7) received three intravenous injections of 80 c.c. of serum, which was followed on the seventh day by mild serum disease, consisting of urticaria and enlargement of lymph nodes, but which persisted for ten days. There was no excessive retention of

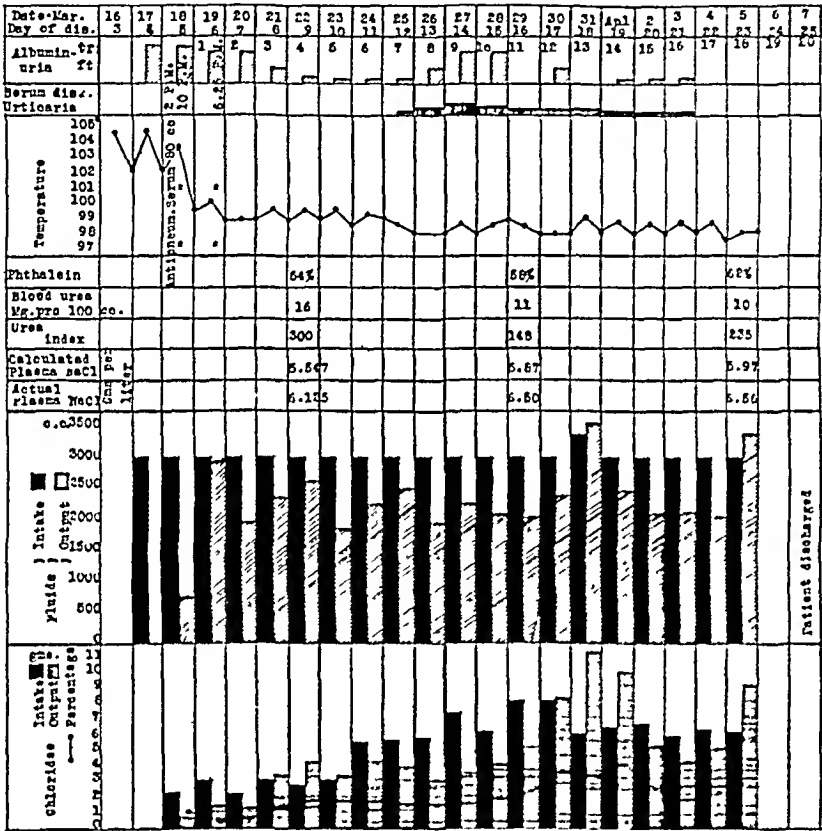


Fig. 4.—E. F., woman, aged 48, with pneumonia, pneumococcus Type 1, with serum disease following the intravenous injection of serum. The course of water and chlorid excretion, the changes in blood urea, the urea index, the plasma chlorids and phenolsulphonphthalein excretion during convalescence from pneumonia complicated by serum disease. The severity of the serum disease is represented by the height of the blocks in that section.

chlorids or water, but the patient was incapable of concentrating the chlorids in the urine and excreted fair quantities of chlorids in low concentration. This is well illustrated in Figure 4. It will be seen that on two occasions, March 31 and April 5, when chlorids were excreted in excess of the intake, an actual diuresis occurred.

In Case 10 the same type of excretion was observed. In both instances there were albuminuria and cylindruria, which disappeared after the subsidence of the serum disease. In this group, therefore,

the serum disease was accompanied by a hyposthenuria. A study of the blood chlorids in Case 7 showed that they were always high before, during and after the attack of serum disease, but tended to rise during the serum disease from 6.25 gm. per liter to 6.5 gm. per liter. In this group, therefore, it is evident that there is a retention of chlorids in the blood, though it is impossible to exclude the tissues as well. They are, however, excreted through the kidneys only in dilute solution, which results in what Schleyer has termed hyposthenuria. It is possible that in these two instances there was some previous injury to the kidney which resulted in this type of excretion. But so far as could be determined from subsequent study of one of these patients, these alterations were not persistent.

COMMENT

These studies show very definitely that during serum disease there is often a marked but transient retention of chlorids and of water, associated frequently with slight albuminuria and cylindruria and occasionally with impairment of the excretion of phenolsulphonephthalein. In five of the ten cases there was obvious edema with gain in weight. In the other cases there was no edema and no gain in weight. In the first group it is probable, since the plasma chlorids were below normal, that some disturbance occurred primarily in the tissues during the intoxication, which cause a retention of salt and water in this situation, and was associated with a generalized edema. There may also have been some functional impairment in the excretory action of the kidneys. In the second group, in which the plasma chlorids were high, the disturbance consisted principally in the impaired elimination of chlorids and the inability to concentrate these organic salts in the urine. In the two cases in this group edema was not observed.

INFLUENCE OF AGE AND SEX ON HEMOGLOBIN

A SPECTROPHOTOMETRIC ANALYSIS OF NINE HUNDRED AND NINETEEN CASES *

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To the thoughtful clinician it has long been a matter of keen regret that the very examination of the blood which is perhaps most frequently made in routine practice, namely, the estimation of the percentage of hemoglobin, is the one from which we generally derive the most unsatisfactory results. Aside from the very glaring defects in some of the instruments in common use, this has been due to the fact that we have had few accurate data as to the variations in the amount of hemoglobin at different ages. What knowledge we possess on the subject dates from the work of Leichtenstern.¹ This author recognized very clearly that before any conclusions could be drawn as to whether a person of a given age and sex had a normal amount of hemoglobin, it was first necessary to determine the norm for that age and sex. In addition to studying the effects of a number of other physiologic conditions on the hemoglobin content of the blood, Leichtenstern made determinations of the hemoglobin in a number of normal persons of both sexes, and at various ages, in order to determine the variations due to age and sex. Practically all of the knowledge of these factors which we possess is derived from this work. There are, however, a number of reasons why Leichtenstern's work is inadequate. In the first place, at that time it was not possible to crystallize human oxy-hemoglobin, and therefore his results were only relative. Any absolute figures attributed to him have been obtained by using the extinction coefficients given by him with a factor obtained years after by others. Since, as was shown later by Butterfield, this factor may vary materially with slightly different conditions of experiment, and especially with different instruments, the propriety of this is more than questionable.

In addition, his observations were made on too few persons to give anything more than approximate results, a fact which he himself plainly states. For example, he examined no infants on the first day of life, and his values for infants up to four days are based on only four determinations, three in boys and one in a girl, the youngest being

* Submitted for publication June 13, 1916.

1. Leichtenstern: Untersuchungen über den Haemoglobingehalt des Blutes in gesunden und kranken Zuständen, 1878.

only 36 hours old. For three age periods (from 51 to 56, from 56 to 60 and over 60) he based his figures on a total of only five cases, for both men and women, so that in these instances the figures for one sex are based on the examination of only two persons. Such results are, of course, entirely unreliable. He did not carry his age periods beyond the sixtieth year.

In view of the inadequacy of Leichtenstern's work, and in view of the absence of any extended investigations, with methods of precision, bearing on these points, it seemed very necessary that the entire matter should be reinvestigated on an amply large material, and employing a method of acknowledged and demonstrable accuracy.

The fact that Leichtenstern's work deals entirely with persons living under conditions as they then existed in Germany, and who might or might not present hemoglobin concentrations identical with those of our patients in America, seemed a further reason for undertaking this research.

METHOD OF STUDY

Of all the methods for the estimation of hemoglobin which have been proposed, the spectrophotometric is unquestionably the most accurate. In addition to its great accuracy it possesses the important advantage of requiring only a small amount of blood, and the technic of using the spectrophotometer, when once acquired, is relatively simple, although somewhat time-consuming. Even in the comparatively primitive form, as used by Vierordt, it was a very exact instrument, and in the improved form, as used by Huefner, it is even more so. Our instrument was a new Huefner apparatus, as made by Albrecht of Tübingen.

Some months of time were devoted to attaining the necessary familiarity with the instrument so as to insure a sufficiently high degree of accuracy. A critical study of the possible sources of error was made, which resulted in the development of a technic which could be depended on to give results of a marked degree of uniformity and exactness. Through the kindness of Prof. George Dreyer, head of the department of physiology, the facilities of the physiologic laboratory were placed at our disposal. In addition, it is a pleasure to acknowledge our indebtedness to him for much advice and assistance during this preliminary work, which was begun early in 1914.

QUANTITATIVE SPECTROPHOTOMETRIC DETERMINATION OF HEMOGLOBIN: PRINCIPLES INVOLVED

Without attempting to go into the general subject of spectrophotometric examinations, the principles of which must be assumed to be already known, it may be in place to give briefly the salient points. For each colored substance the ratio, concentration to extinction

coefficient, is a constant. This constant is known as the absorption ratio. This law is generally expressed $C/E=A$. The concentration C in the case of blood is the number of grams of oxyhemoglobin in 1 c.c. of the solution examined. The extinction coefficient is the reciprocal of the thickness of solution required to reduce light of the intensity one to the intensity one tenth. In the Huefner apparatus the thickness of the layer of solution remains constant, and E is determined by measuring the intensity of the remaining light. This is effected by rotation of the analyzing with respect to the polarizing Nicol. Now it can be readily shown that the extinction coefficient, E , is equal to $-2 \log. \cos. O$, where O is the angle of rotation just referred to. In order to obtain E we measure the angle of rotation, O , necessary to produce equality in the upper and lower fields. This angle is read off on a vernier, and from this the extinction coefficient, E , is computed. Buerker has computed a curve of extinction coefficients for angles from 60 to 82 degrees, which greatly facilitates this computation. For solutions of one and the same substance, in our case oxyhemoglobin, the concentrations are directly proportional to their respective extinction coefficients, so that these are used as a convenient method of expressing relative concentrations. To convert relative into absolute values a solution of oxyhemoglobin of known strength must be prepared, its extinction coefficient, E , determined, and then $A=C/E$, or $C=E \times A$. In other words, the extinction coefficient of any solution multiplied by the absorption ratio thus obtained gives the absolute concentration of the solution. This absorption ratio was determined by Huefner for oxyhemoglobin for the spectral region from 531.5 to 542.5, and found to be 0.001312. Butterfield² found it to be 1.18×10^{-3} for the spectral region from 533.5 to 542.

The exact position in the spectrum, the width of slit and several other factors exercise a great influence on the value of A , as Butterfield has shown, so that it is essential, in order to be sure of the results, for each investigator to determine the value of A for his exact conditions of experiment. Since the publication of the preliminary report of this research we have done this, and the absolute values, as given in this paper, represent the relative values previously given multiplied by the factor A , with, of course, the proper correction for dilution. It is unnecessary to describe the Huefner apparatus. We had a special dark room at our disposal and the entire apparatus was further enclosed in a large hinged light-proof case, so constructed that when in use no extraneous light could reach the eye. This is a matter of much impor-

2. Butterfield, E. E.: Ueber die Lichtextinktion, das Gasbindungsvermögen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und krankhaften Zuständen, *Ztschr. f. physiol. Chem.*, 1909, lxii, 173.

tance, since eye fatigue is the principal source of error in the method. The sector scale was calibrated in the usual manner, so that the divisions on it could be converted into wave lengths. To assure ourselves that the positions actually chosen really represented the positions of maximum and minimum absorption we determined the degree of absorption for the entire area. The positions found were from 542 to 534 and from 566.5 to 558.5. Our collimator slit was set at 0.05 mm., and remained unchanged throughout all the work. The eye piece slit was set at 8.

DETERMINATION OF THE EXTINCTION-RATIO (E'_o/E_o)

It is well known that Vierordt and his school have, through a long series of investigations, enunciated the law on which the qualitative spectrophotometric determination of hemoglobin, as well as its derivatives, is based. If E' be the extinction coefficient in one part of the spectrum, and E be the extinction coefficient in the other part of the same spectrum, then the extinction ratio E'/E is constant for one and the same hemoglobin derivatives, even at different concentrations; while on the other hand, the ratio E'/E is different for each derivative and characteristic of it. For oxyhemoglobin the ratio E'_o/E_o has been found by Huefner to be 1.578, or as it is generally expressed in round figures, 1.58.

Bohr³ has called into question the identity of hemoglobin from different sources and considers that there are several hemoglobins. His researches do not bear out the contention of Huefner that the ratio E'_o/E_o is one and the same under identical conditions of experiment.

Aron and Müller⁴ in 1906 also found an inconstancy of this ratio. On the other hand, Butterfield, using the Huefner apparatus, conducted an extensive series of experiments, and came to the conclusion that the light extinction, iron content and oxygen-binding capacity of human hemoglobin are, within the limits of error of the method employed, constants. He further found that these constant values applied, not only to the blood of normal human beings, but also to those bloods derived from patients with anemia, chlorosis, scorbutus and pseudoleukemia. While it was not the principal purpose of this research to determine the constancy of this coefficient, yet inasmuch as the value of the spectrophotometric qualitative analysis depends on the extinction ratio, it was felt to be highly desirable to determine this constant anew under the conditions of our experiments, in spite of the

3. Bohr: Nagel's Handbuch der Physiologie des Menschen, i, 51 (Bibliography).

4. Aron and Müller: Ueber die Lichtabsorption des Blutfarbstoffs, Arch. f. Physiol., 1906, Suppl., p. 109; Ztschr. f. physiol. Chem., 1906, lvi, 443.

apparently conclusive work of Butterfield. To this end, in each and every observation, readings were taken not only in the position of maximum, but in the position of minimum absorption, and from these values the extinction ratio, that is, $E'o/Eo$, was calculated for each determination. Because of the large number of determinations made by us, it was felt that the average of all of these would give a very close approximation to the real value. Every observation is included except those in which the reading in the region between the bands was below 60 degrees, since we, in common with all observers, found the accuracy in reading diminishes rapidly below this point. These observations numbered in all 838, and the ratio was found to be perfectly constant within the limits of error of the method, and to average 1.5813. Our results, therefore, corroborate in fullest measure those of Huefner and Butterfield, not only in regard to the constancy of the extinction ratio, but also in regard to its actual value. Huefner's⁵ determinations average 1.578, as against our value of 1.5813.

CONSTRUCTION AND CALIBRATION OF PIPET

It is obvious, in view of the high degree of accuracy attained in the actual reading of the spectrophotometer, that the error involved in measuring and diluting the blood is likely to be several times as great as the error of reading. Leichtenstern recognized this, and came to the conclusion that it might be ten times as great. Our preliminary work led to the same conclusions, and to reduce the error in obtaining and diluting the blood to a minimum, considerable experimentation and thought were given to the question of a suitable pipet. In this matter we were rendered invaluable aid by Professor Welker, to whose kindness we are indebted for the construction and calibration of the pipet, and to whose advice and skill the accuracy of this part of the work is entirely due.

In its final form the pipet consisted of a piece of heavy thermometer tubing with thick walls, but of fine caliber, and yet sufficiently large that when it was filled with blood and held vertically the column would flow down with that degree of rapidity best suited for accurate measurement. It was approximately 7 inches in length, with a circular mark about 4 inches from the tip, the latter being drawn out so as to constrict the opening to the least possible extent. Two separate calibrations of the pipet were made, with defibrinated blood, in the most careful manner, and the average of the two determinations gave the weight of blood delivered by it as 0.03865.

5. Huefner, G.: Neue Versuche zur Bestimmung der Sauerstoffkapazität des Blutfarbstoffs, Arch. f. Physiologie, 1894, p. 130.

The specific gravity of the blood was determined with two separate pycnometers, each of a different type, and found to be 1.0601 and 1.0597 respectively, the average being 1.0599. The volume of blood delivered by the pipet was, therefore, $0.03865/1.0599 = 0.03646$ c.c. It was found that this amount could be readily obtained from either the finger in adults or ear in children without resorting to undue manipulation. The advantages of having the pipet of a larger capacity than those in common use are obvious.

TABLE 1.—COMPARISON OF TWO DILUTIONS TO DETERMINE ACCURACY OF PIPET

Solution A		Solution B	
77.9	77.8	77.4	78.0
77.2	77.5	78.0	78.0
77.9	77.6	77.5	77.4
77.4	77.7	77.4	77.6
77.8	77.9	78.0	77.5
77.6	77.6	77.6	77.4
77.9	78.0	77.4	77.4
77.4	77.4	77.4	77.7
78.0	77.6	77.4	77.9
77.4	77.5	77.4	77.6
776.6	776.6	775.5	776.5

A further check of the accuracy of the calibration was made in the following way. A pipetful of defibrinated blood was added to 4 c.c. of 0.1 per cent. sodium carbonate solution, giving a dilution of 1 in 110.709. Similarly 1 c.c. of the same blood was added to 109.709 c.c. of sodium carbonate solution, and these two dilutions were then compared spectrophotometrically. The result of the comparison is shown in Table 1.

The averages were 77.66 and 77.60, respectively with the two solutions, and the extinction coefficients were 1.340 and 1.336 respectively.

The concentrations of the two specimens, as measured by these two methods, are proportional to their extinction coefficients, that is, the dilutions are to each other as 1.340 to 1.336, which gives further evidence of the accuracy of the pipet calibration. One and the same pipet was used throughout all the work. All dilutions were carried on in precisely the same manner, using a Mohr normal 5 c.c. pipet for that purpose. In the comparison given a Mohr 1 c.c. normal pipet and a normal buret were used, all bearing the standardization mark of the German Reichsanstalt.

METHOD OF OBTAINING AND DILUTING THE BLOOD

Considerable preliminary experimentation convinced us that the most satisfactory source of blood, when uniformity is the great desideratum, is the finger pulp. We used in all cases the middle finger of the left hand, except in young children, in whom the lobe of the ear was chosen. The manner of making an incision is of importance. We used cataract knives of the best quality, which were sent to the maker at short intervals for sharpening. A deep stick gave a very large flowing drop of blood, from which the pipet was filled to a point just a trifle above the mark, and then with the pipet held vertically the column was allowed to sink down exactly to the mark, the excess of blood on the tip being removed by the thumb and forefinger. This blood was then blown into 4 c.c. of 0.1 per cent. sodium carbonate solution, which had been previously measured with a Mohr 5 c.c. normal pipet into a 50 c.c. long-necked, glass-stoppered flask. Our pipet was graduated as a delivery pipet, and by blowing with force each time for ten seconds and withdrawing the tip of the pipet from the fluid, while still blowing, a high degree of uniformity was secured, as will be seen from the accuracy determinations below. The solution must be absolutely clear.

The diluted blood was then thoroughly shaken to ensure complete oxygenation, which is considerably facilitated by the relatively large size of the flask. The blood solution was now transferred into the *Trögchen* of the apparatus, which was covered with a glass slip to exclude atmospheric influences, and ten readings were taken, five on each side of the vernier scale, in the selected position (542.0 to 534.0). In all cases readings were also taken in that position of the spectrum lying between the bands (566.5 to 558.5), so that the extinction ratio could be instantly calculated, and any possible deterioration in the specimen thus disclosed. We regard this as an indispensable precaution, since it obviates the possibility of any error due to a reduction of the oxyhemoglobin, or to a possible partial conversion into methemoglobin.

SOURCES OF ERROR

In any research having to do with the establishing of norms, it is highly important to be orientated as to the possible sources of error and the magnitude of these. In our work we must consider the following: (1) error in the calibration of the pipet; (2) error in taking and diluting the blood; (3) error due to a possible reduction of the oxyhemoglobin to reduced hemoglobin or methemoglobin; and (4) error in reading.

1. *Error in Calibration.*—Any error in this respect is of course a constant one. As stated above, the volume of our pipet was obtained by

taking the mean of two calibrations, agreeing closely with each other. In addition this was checked, as above stated, by comparing spectrophotometrically the dilution, as made by our pipet, and a second similar dilution made with normal pipets standardized by the German Reichsanstalt. Two dilutions made in this way gave extinction coefficients, as we have already seen, of 1.340 and 1.336, respectively. The close agreement of these figures, in addition to the trifling variations of the figures of the two standardizations, makes it sufficiently obvious that the error of calibration is an entirely negligible factor. Since any error would be constant, it could have no effect on the relative values.

2. *Error in Taking and Diluting the Blood.*—This is, of course, a variable error. In the calibration of our pipet we proceeded in the following manner: A weighing bottle, with a roll of filter paper, was first weighed, and after the pipet had been filled with blood in the usual manner, this was blown into the bottle, the excess being wiped off on the paper and contents weighed again. Two determinations were thus made, and the weights obtained may be used as an index of the error involved in measuring the blood. They were 0.0385 and 0.0388.

Our pipet was therefore of such construction as to admit of exceedingly accurate measurements.

3. *Error Due to Deterioration of the Oxyhemoglobin.*—As we have already indicated, by taking readings in the positions of both maximum and minimum absorption, we could at once calculate the extinction ratio $E'o/Eo$ for each observation, so that no appreciable deterioration could occur without being detected immediately. All of our readings were made shortly after taking the blood, so that any deterioration was a priori, improbable. Further to test the degree of deterioration dilutions were made in the usual manner, and tested spectrophotometrically, the first immediately, the second at the end of one hour, and the third at the end of two hours. The extinction coefficients thus obtained were (immediately) 1.300, (one hour) 1.290, (two hours) 1.297. This check was made repeatedly, and in no instance did we find a deterioration sufficient to be detected, within two hours' time.

4. *Error in Reading.*—The construction of the Huefner apparatus is such that the readings can be taken with great accuracy after sufficient practice. This will be apparent from a mere inspection of the readings above given. The Gauss method, which Leichtenstern,¹ Reinert⁶ and Buerker⁷ have employed, enables us to determine the average and probable errors.

6. Reinert: Die Zaehlung der Blutkoerperchen, Leipzig, 1891.

7. Buerker: Tigerstedt's Handbuch, Vol. 2.

Taking a typical example, we find in one accuracy determination (Jan 1, 1915) the readings given in Table 2.

TABLE 2.—READINGS IN AN ACCURACY TEST OF HUEFNER APPARATUS *

Number Readings	Square of Variation	Variation from Average	Reading Left	Reading Right	Variation from Average	Square of Variation
1	0.0289	+0.17	76.6	76.6	+0.17	0.0289
2	0.0529	−0.23	76.2	76.4	−0.03	0.0009
3	0.0049	+0.07	76.5	76.5	+0.07	0.0049
4	0.0169	−0.13	76.3	76.6	+0.17	0.0289
5	0.1849	−0.43	76.0	76.6	+0.17	0.0289
	0.2885	0.0925

* Average of ten readings 76.43. $Sd^2 = 0.3810$.

Let d equal the variation from the average.

Let Sd^2 equal the sum of the squares of the individual variations.

Let F_m equal the average error of the average value.

Let N equal the number of observations.

The average error of the average value

$$F_m = \sqrt{\frac{Sd^2}{n(n-1)}} = \sqrt{\frac{0.3810}{10(10-1)}} = \pm 0.0653$$

The angular error is thus plus or minus 0.0653 degrees.

$$\begin{aligned} \text{Now, } 76.43 + 0.0653 &= 76.4953 = \text{approximately } 76.50 \\ 76.43 - 0.0653 &= 76.3647 = \text{approximately } 76.36 \end{aligned}$$

Corresponding to these angles we have the extinction coefficients:

$$\begin{aligned} E'o \text{ of } 76.50 &= 1.264 \\ E'o \text{ of } 76.36 &= 1.256 \end{aligned}$$

If we calculate by the same method the probable error, we find it to be $\pm 0.0653 \times 0.6745 = 0.0440$.

These results justify the conclusion that with ten readings the error of the average of these readings is exceedingly small, and can be safely disregarded.

ACCURACY DETERMINATIONS

Before making any of our record observations, we instituted a series of determinations extending over some time to assure ourselves that the necessary amount of familiarity with the method had been secured to attain a high degree of precision. We employed the following method: A pipetful of defibrinated blood was diluted in the usual manner with 4 c.c. of sodium carbonate solution, and the pipet washed and dried. A second pipetful of the same blood was then taken and diluted in the same way. These were then examined spectrophotometrically, ten readings being taken and the same *Trögchen* being used

in both cases. A typical determination of this sort, made on Oct. 30, 1914, is given in Table 3.

TABLE 3.—A TYPICAL ACCURACY TEST OF THE METHOD

Solution A		Solution B	
78.1	77.9	77.8	77.9
78.4	78.5	78.0	78.0
78.2	77.9	78.0	78.2
78.7	78.3	78.6	78.5
78.0	78.0	78.2	77.9
391.4	390.6	390.6	390.5

The averages were 78.20 and 78.11 for the two solutions, respectively, and the extinction coefficients were 1.379 and 1.372 respectively.

To determine the effect of increasing practice on the degree of accuracy, another series of tests were made several months later, some hundreds of determinations having been made in the interim. A typical series is here given in which on Feb. 7, 1915, three successive dilutions were made in the manner above indicated. In dilution No. 1 the extinction coefficient 1.300 was obtained, and in dilutions Nos. 2 and 3, 1.290 and 1.297 were respectively obtained.

It is obvious from these figures that the degree of accuracy attained is almost precisely the same from the beginning of our recorded observations. In order to eliminate the possibility of any self-suggestion in the reading of similar dilutions, we made further tests in the following manner: One pipetful (A) of blood was diluted with 4 c.c. of sodium carbonate solution, a second (B) with 4.5 c.c. of the same fluid. Calculation shows that the concentrations of these two solutions are to each other as 124.42 to 110.71. These two solutions were then examined spectrophotometrically with the results shown in Table 4.

TABLE 4.—ACCURACY TEST ON DIFFERENT CONCENTRATIONS OF THE SODIUM CARBONATE SOLUTION

Solution A		Solution B	
78.7	78.5	75.6	76.2
78.8	78.7	76.3	75.9
78.4	78.7	76.5	76.2
78.5	78.4	76.5	76.4
78.3	78.6	76.1	76.3
392.7	392.9	381.0	381.0

The averages were 78.56 and 76.20 with the respective solutions, and the extinction coefficients were 1.405 and 1.245.

Taking the ratios, we find $1.405/1.245 = 1.128$,
and $124.42/110.71 = 1.124$.

In other words, the two solutions were so prepared that their concentrations were to each other as 1 to 1.124, while the observed concentrations were as 1 to 1.128.

A considerable number of such tests were made with similar results. Our study of the spectrophotometric method leads us to the conclusion that it is capable of quite an extraordinary degree of accuracy, provided that the investigator have the necessary familiarity with the apparatus. With adequate practice, the error of observations made with the precautions we have used, probably does not exceed 1 per cent. We also made determinations, using thirty readings instead of ten, but were unable to increase the accuracy by so doing. Indeed, there is a real danger of lessening it by too many readings, since there is a distinct risk of overtiring the eye, which produces a rapid diminution of accuracy.

In all of these tests for the purpose of determining the accuracy of the spectrophotometric method as employed by us, precisely the same conditions obtained as in the routine determinations. The results, therefore, show the accuracy really attained under our actual working conditions, and not that theoretically possible, or attainable only under especially favorable circumstances.

SELECTION OF MATERIAL

Inasmuch as the concentration of hemoglobin may vary to a considerable degree in individuals who may regard themselves as being perfectly well, the greatest care was exercised to ascertain that the individual examined was in reality normal. The numbers available at all ages were sufficiently great to make it a matter of ease to reject all unsuitable observations. In spite of the painstaking efforts to secure perfectly normal subjects, no attempt was made at any especial selection. In other words, individuals remarkable for their strength or physical development were only chosen as they happened to fall naturally within the scope of our observations. To avoid any possible error due to a preponderance of some particular type of subject, our observations were fairly evenly distributed among all walks of life, so that it is believed that the results represent a fair average. All observations were excluded if the individual had recently had any sickness, was evidently in poor nutrition, or felt below par in any way. In the case of babies and young children only such were taken as were evidently thriving, gaining normally in weight, and who had not had any sickness of consequence within a year. By far the larger part of our babies were breast fed.

In the age groups included between the 10th and 30th years a considerable number of observations were made on schoolchildren and college students, and these observations were for the most part made shortly after the summer vacation, since the general state of health and nutrition was at this time presumably at its best. In addition to the above precautions, which are of considerable importance if the resulting figures are to establish really normal values, care was taken, as will be evident at a glance from the table, to have substantially the same number of observations in each of the various age groups, and still further to have approximately the same number for each sex. The minimum number of observations on which any figure for an age period is based is thirty, except in the comparison of the sexes, in which, of course, the number for each sex is one half the total for the group. Our results are based on a study of 919 persons, 464 male, and 455 female. With the exception of a few children, all of the determinations were made in the midafternoon hours.

METHOD OF PREPARATION OF HEMOGLOBIN

Several hundred cubic centimeters of blood were obtained from each of two healthy adults by venepuncture, and defibrinated as usual. This was then centrifugalized and the corpuscles washed several times, thus removing the major portion of the serum proteins. It was then laked by the addition of ether, added in successive small portions until a clear solution was obtained. If the solution was too viscid, sufficient water was added to bring it to the proper degree of fluidity. The blood was then treated with an approximately equal volume of aluminum cream, as suggested by Marshall and Welker.⁸ The aluminum cream was prepared in the manner described by Tracy and Welker.⁹ After thorough mixing and filtering, the filtrate being perfectly clear, this was placed in a refrigerator, cooled down to -3 or -4 C. and then treated with absolute alcohol until the percentage of the latter equaled 25 or 30. This was allowed to remain at the above temperature until crystallization was completed. The mass of hemoglobin crystals on the filter was then transferred to a weighing bottle of known weight, and the moist weight of the mass of crystals determined. From this a suitable sample was removed for spectrophotometric examination, placed in a very small beaker, and then dissolved in a very little 0.1 per cent. sodium carbonate solution, and transferred quantitatively to a 10 c.c. standardized flask, which was then filled up

8. Marshall and Welker: The Precipitation of Colloids by Means of Aluminum Hydroxid, *Jour. Am. Chem. Soc.*, 1913, xxxv, 820

9. Tracy and Welker: The Use of Aluminum Hydroxid Cream for the Removal of Albumin in Nitrogen Partition in Urinary Analysis, *Jour. Biol. Chem.*, 1915, xxii, 55.

to the mark with the same solution. A preliminary reading was made to determine the approximate concentration, and with this as a guide the solution was further diluted so as to bring the readings in the region between 60 and 80 on the scale, since this is the position of optimum accuracy. Readings were then taken in both positions in the spectrum in the way already described.

The weighing bottle with its contents was then placed in a desiccator over sulphuric acid, where it remained until it attained a constant weight. From this the dry weight of the sample was calculated, and this weight, divided by the dilution, gives the concentration, that is, the amount of hemoglobin in 1 c.c. of the solution tested. To make sure that no reduction or conversion of the oxyhemoglobin had taken place, readings were invariably taken with great care in both regions of the spectrum. The ratio of these extinction coefficients gave a constant result of 1.581, within the allowable limits of error. Blood was obtained from two separate individuals, and crystals prepared as above described from each,

DETERMINATIONS OF THE ABSORPTION RATIO (A'_o)

In the preliminary report¹⁰ of this work all the values as there given were relative only, that is, they represented the extinction coefficients obtained by taking $-\log. \cos.^2$ of the angles of rotation. In order to convert these relative into absolute values, that is, to determine the actual hemoglobin concentration, it is necessary to multiply the extinction coefficients by a constant factor, namely, the absorption ratio A'_o . While the value of A'_o has been determined by several authors, notably Huefner, later researches made by Butterfield² in Huefner's laboratory give a quite different value. Moreover, Butterfield has shown that the absorption ratio may vary considerably with very slightly different conditions of experiment.

Since the accuracy of the absolute values depends on the correctness of the absorption ratio, it was felt to be important to establish this for our conditions of experiment.

In order to do this it was necessary first to prepare pure crystalline human hemoglobin. After the purity of this had been established spectrophotometrically by determining the extinction ratio, a solution of known concentration was made up. This solution was then placed in the spectrophotometer, the angle of rotation measured and from this the extinction coefficient ($E'o$) of the solution calculated. Since the concentration is known, the absorption ratio ($A'o$) can be determined from the formula $A'o = C/E'o$.

For the preparation of the hemoglobin I am indebted to the courtesy of Professor Welker, and the results are extracted from a joint

10. Williamson: Jour. Am. Med. Assn., 1915, lxv, 302.

paper in process of preparation, in which, in addition to human hemoglobin, a number of hemoglobins from different animals are being studied, Professor Welker undertaking the preparation of them, the present author determining the optical constants.

HUMAN HEMOGLOBIN

Crystallization No. 1: The dry weight of the specimen was 0.0997 gm. This was dissolved in 0.1 per cent. sodium carbonate solution, and made up to 10 c.c. in a standardized flask. From this solution three subdivisions were made, using 1 c.c. of the above for each, and diluting by adding 5.5 c.c. of sodium carbonate solution, making the total dilution 1 in 65.

Each of these subdivisions was placed in the *Trögchen* and ten readings taken in each of the two positions in the spectrum already alluded to. Table 5 gives the results.

TABLE 5.—DETERMINATION OF $A'o$

Subdivision	Average of Ten Readings (542.0 to 534.0)	Extinction Coefficient $E'o$	Average of Ten Readings (566.5 to 558.5)	Extinction Coefficient E_o
No. 1	77.19	1.309	67.40	0.831
No. 2	77.36	1.320	67.04	0.818
No. 3	77.21	1.310	68.13	0.853

The average $E'o = 1.313$; and the average $E_o = 0.836$. The concentration $= 0.0997/65 = 0.001534$. $A'o = C/E'o = 0.001534/1.313 = 0.001168$. $A_o = C/E_o = 0.001534/0.836 = 0.001835$.

That the solution was actually a pure oxyhemoglobin solution is shown by the extinction ratio. $E'o/E_o = 1.313/0.836 = 1.571$.

Crystallization No. 2: The dry weight of the specimen was 0.02479 gm. This was dissolved in 0.1 per cent. sodium carbonate solution, and made up to 10 c.c. in a standardized flask. From this solution three subdivisions were made until the final dilution was 1 in 17.

TABLE 6.—DETERMINATION OF $A'o$

Subdivision	Average of Ten Readings (542.0 to 534.0)	Extinction Coefficient $E'o$	Average of Ten Readings (566.5 to 558.5)	Extinction Coefficient E_o
No. 1	75.73	1.216	65.91	0.778
No. 2	76.25	1.248	66.01	0.782
No. 3	75.62	1.210	66.07	0.784

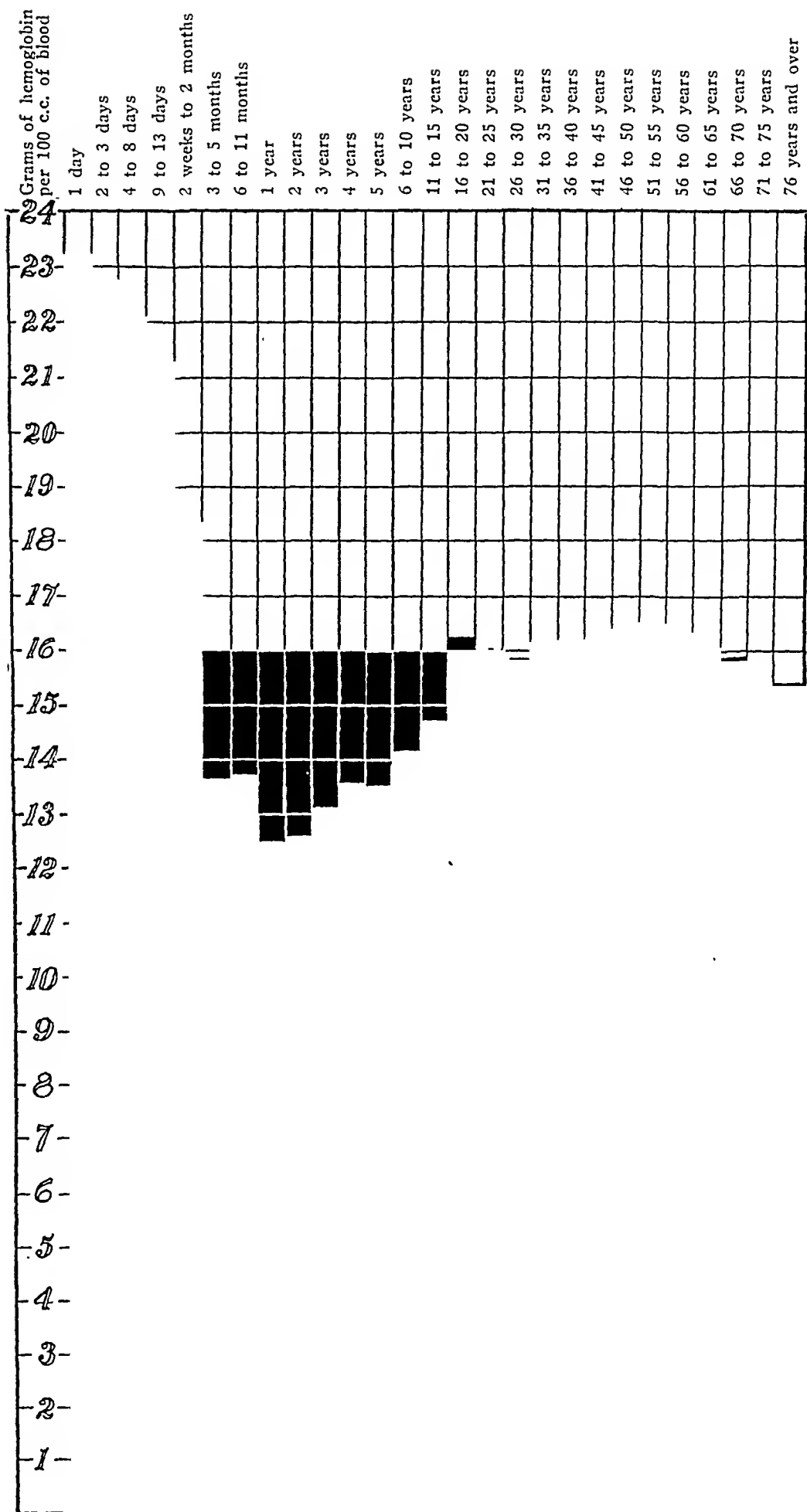


Fig. 1.—Grams hemoglobin per 100 c.c. of blood in persons ranging in age from 1 day to over 76 years.

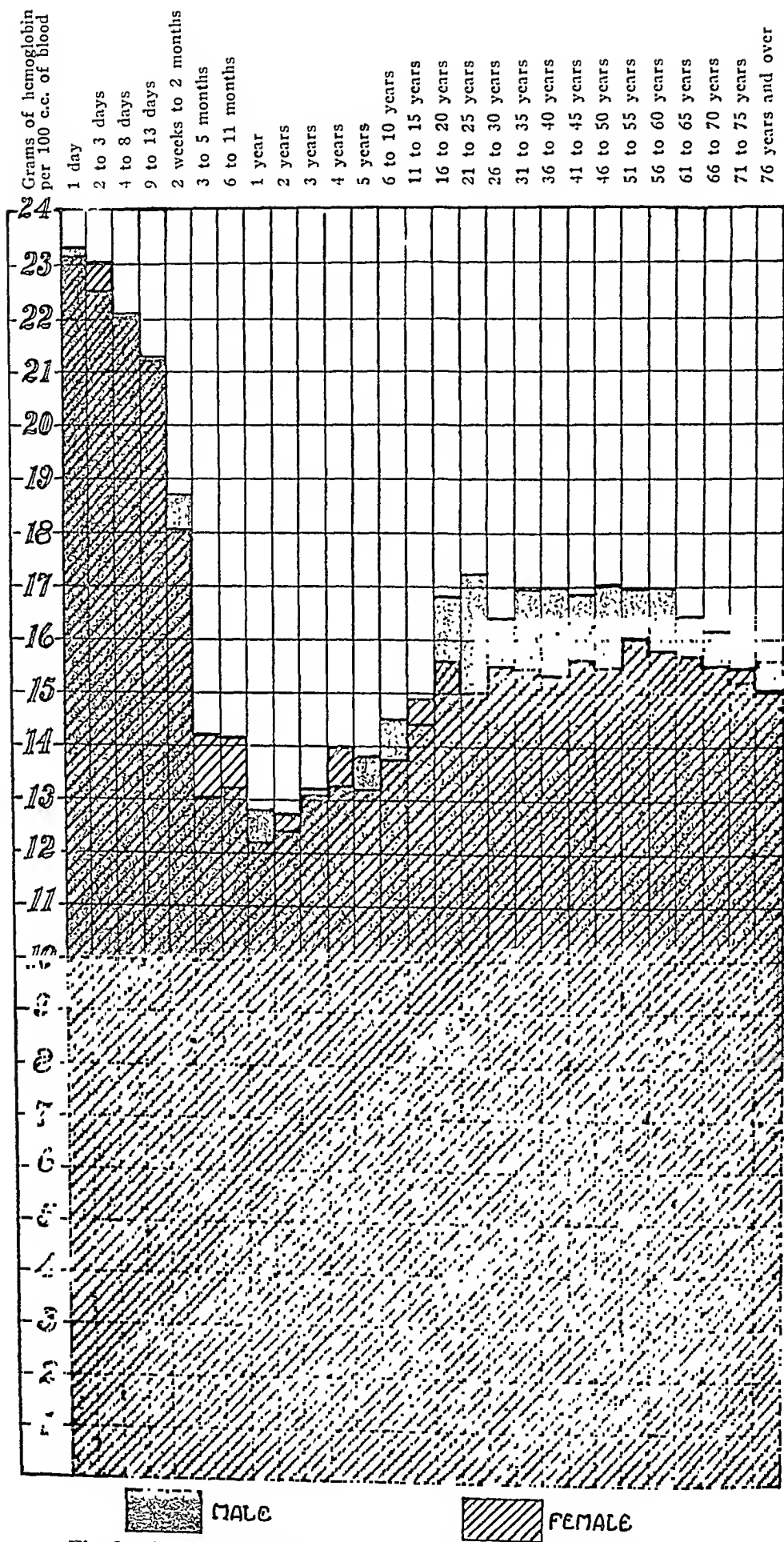


Fig. 2.—Grams hemoglobin per 100 c.c. of blood in the male and in the female, for the ages ranging from 1 day to over 76 years.

The average $E'o = 1.225$; and the average $Eo = 0.781$. The concentration $= 0.02479/17 = 0.001458$. $A'o = C/E'o = 0.001458/1.225 = 0.001190$. $Ao = C/Eo = 0.001458/0.781 = 0.001867$.

That the solution was actually a pure oxyhemoglobin solution, is shown by the extinction ratio. $E'o/Eo = 1.225/0.781 = 1.569$.

TABLE 7.—RESULTS OF EXAMINATION

Age	Extinction Coefficient, Dilution 1:110.71			Grams of Hemoglobin per 100 C.c. of Blood			Number of Cases		
	Male	Female	Both	Male	Female	Both	Male	Female	Both
1 day.....	1.7859	1.7763	1.7813	23.31	23.19	23.25	16	15	31
2 to 3 days.....	1.7239	1.7657	1.7454	22.50	23.05	22.78	15	16	31
4 to 8 days.....	1.6965	1.6936	1.6949	22.14	22.11	22.12	15	18	33
9 to 13 days.....	1.6366	1.6342	1.6355	21.36	21.33	21.35	15	15	30
2 weeks to 2 mos..	1.4329	1.3822	1.4109	18.70	18.04	18.42	15	15	30
3 to 5 months.....	1.0019	1.0915	1.0467	13.08	14.25	13.66	16	16	32
6 to 11 months.....	1.0129	1.0876	1.0499	13.22	14.19	13.70	18	15	33
1 year.....	0.9806	0.9367	0.9599	12.80	12.23	12.53	18	16	34
2 years.....	0.9530	0.9727	0.9631	12.44	12.70	12.57	16	17	33
3 years.....	1.0121	1.0041	1.0081	13.21	13.11	13.16	15	16	31
4 years.....	1.0177	1.0710	1.0435	13.28	13.98	13.62	16	15	31
5 years.....	1.0596	1.0166	1.0375	13.83	13.27	13.54	17	18	35
6 to 10 years.....	1.1163	1.0498	1.0861	14.57	13.70	14.18	18	15	33
11 to 15 years.....	1.1090	1.1389	1.1252	14.48	14.87	14.69	17	20	37
16 to 20 years.....	1.2879	1.1986	1.2447	16.81	15.64	16.25	16	15	31
21 to 25 years.....	1.3203	1.1515	1.2270	17.23	15.03	16.02	17	21	38
26 to 30 years.....	1.2572	1.1895	1.2169	16.41	15.53	15.88	19	28	47
31 to 35 years.....	1.2975	1.1832	1.2403	16.94	15.44	16.19	16	16	32
36 to 40 years.....	1.3008	1.1771	1.2428	16.98	15.36	16.22	17	15	32
41 to 45 years.....	1.2913	1.1981	1.2432	16.85	15.64	16.23	15	16	31
46 to 50 years.....	1.3080	1.1866	1.2588	17.07	15.49	16.43	22	15	37
51 to 55 years.....	1.2993	1.2323	1.2687	16.96	16.08	16.56	19	16	35
56 to 60 years.....	1.3000	1.2074	1.2537	16.97	15.76	16.36	15	15	30
61 to 65 years.....	1.2612	1.2033	1.2313	16.46	15.71	16.07	15	16	31
66 to 70 years.....	1.2405	1.1890	1.2159	16.19	15.51	15.87	17	15	32
71 to 75 years.....	1.1663	1.1848	1.1750	15.22	15.46	15.34	19	17	36
76 and over.....	1.2003	1.1519	1.1793	15.67	15.04	15.39	30	23	53
							464	455	919

Average for the two crystallizations: No. 1 $A'o = 0.001168$; No. 2 $A'o = 0.001190$; average $A'o = 0.001179$. No. 1 $Ao = 0.001835$; No. 2 $Ao = 0.001867$; average $Ao = 0.001851$.

In common with other observers, we find that the readings in the band ($A'o$) are slightly more accurate than those taken between the bands. In accordance with this all our absolute figures have been calculated by multiplying the extinction coefficient of the readings in this position, $E'o$, by the average absorption ratio, $A'o = 0.001179$. This result, multiplied by the dilution 110.71, gives the concentration, that is, the amount of hemoglobin in each cubic centimeter of blood. For convenience sake we have expressed the results in grams of hemoglobin per 100 c.c. of blood, since this permits us to avoid fractions.

CHARACTERISTICS OF THE AGE CURVE

By far the highest values attained are at birth ($E'o = 1.781 = 23.25$ gm.). This substantiates the results of many investigators. Beginning immediately, there is a very rapid decline, so that from the 3rd to the 5th month the average value is nearly down to the minimum ($E'o = 1.047 = 13.66$ gm.) and is far below the average adult figure. From the 5th month onward there is a relatively gradual diminution, but the actual minimum ($E'o = 0.960 = 12.53$ gm.) is not reached until 1 year, that is in the 2d year of life. During the next year also the same minimum value is found, and only after the child has completed its 2d year does the curve rise again. This is then fairly rapid up to the 16th year, and from the 16th to the 55th year the variations in the different age periods are very slight.

The immediate and rapid decline in the amount of hemoglobin after birth and continuing up to the 6th month, and to a less extent up to the 1st year, is a highly characteristic feature of the age curve. Our results are in this respect in accord with those of Leichtenstern. This decline is quite independent of nutrition, since, as has been above stated, the greatest care was exercised to select only infants that were thriving. Moreover, it is not a question of artificial feeding, since the great majority of our cases, especially up to the 6th month, were breast-fed infants.

A noticeable feature of our curve is the fact that in the age period from 16 to 20 years the values have attained practically the maximum ($E'o = 1.245 = 16.25$ gm.) and from this period to middle age the curve is nearly horizontal. The very highest point is attained in the period from 51 to 55, but the variation in this period from the other younger adult values is insignificant. From the 55th year onward the values decline steadily up to the 75th year ($E'o = 1.175 = 15.34$ gm.). After the 76th year there is a rise, but it is so small as to be negligible ($E'o = 1.179 = 15.39$ gm.). The sharp drop found by Leichtenstern in the period from 55 to 60 is seen, on the basis of our larger number of patients, not to exist. The rise in old age found by him, was based on only five cases in all, whereas our figures for the age period over 76 alone is based on a total of fifty-three persons.

INFLUENCE OF SEX

An inspection of Figure 2 shows that the values from birth up to the 15th year are almost identical for both sexes. At birth the difference is so slight that it can just be portrayed graphically on our curve: male $E'o = 1.786 = 23.31$ gm.; female $E'o = 1.776 = 23.19$ gm.

It must be remembered that the figures on which the values for each sex are based, represent, of course, only one-half the total number of cases. It is, therefore, to be expected that slight variations will occur in these curves to a somewhat larger extent than when the figures for both sexes are combined in a common curve. One especially valuable observation was made on twins, a boy and a girl, both perfectly healthy, of approximately the same weight, whose blood was first examined when they were 5 hours old. The values were almost identical. In order to formulate more precisely the relative values for the two sexes up to the age of puberty we have calculated the average extinction coefficient for each sex separately, as shown by Table 8.

TABLE 8.—INFLUENCE OF SEX ON HEMOGLOBIN IN CHILDHOOD

Age	Sum of Extinction Coefficients, Male	Number Cases	Sum of Extinction Coefficients, Female	Number Cases
1 day.....	28.576	16	26.645	15
2 to 3 days.....	25.858	15	28.252	16
4 to 8 days.....	25.447	15	30.486	18
9 to 13 days.....	24.550	15	24.513	15
2 weeks to 2 months.....	21.593	15	20.733	15
3 to 5 months.....	16.031	16	17.464	16
6 to 11 months.....	18.333	18	16.314	15
1 year.....	17.650	18	14.988	16
2 years.....	15.248	16	16.536	17
3 years.....	15.181	15	16.071	16
4 years.....	16.284	16	16.065	15
5 years.....	18.014	17	18.299	18
6 to 10 years.....	20.093	18	15.747	15
11 to 15 years.....	18.853	17	22.779	20
	281.711	227	284.892	227

The average extinction coefficient for males is $1.241 = 16.20$ gm.; for females, $1.255 = 16.38$ gm.

From these averages it is clear that the variations in hemoglobin due to sex are, up to the 16th year, hardly greater than the error in the method, and may, for all practical purposes, be neglected.

On the other hand, from the 16th to the 70th year the sex differences make themselves plainly manifest. While the variations are, for either sex, relatively slight within these periods, the values for women are, in every instance, considerably lower than those for men. From the 50th to the 70th year, that is, after the cessation of menstruation, it should be noted that the differences between the sexes still exists, although to a less marked degree than during the child-bearing period.

Table 9 shows the differences due to sex from the 16th to 70th year.

TABLE 9.—INFLUENCE OF SEX ON HEMOGLOBIN IN ADULT LIFE

Age	Sum of Extinction Coefficients, Male	Number Cases	Sum of Extinction Coefficients, Female	Number Cases
16 to 20 years.....	20.606	16	17.979	15
21 to 25 years.....	22.445	17	24.181	21
26 to 30 years.....	23.887	19	33.308	28
31 to 35 years.....	20.759	16	18.932	16
36 to 40 years.....	22.114	17	17.657	15
41 to 45 years.....	19.370	15	19.169	16
46 to 50 years.....	23.778	22	17.800	15
51 to 55 years.....	24.688	19	19.718	16
56 to 60 years.....	19.500	15	18.116	15
	202.147	156	186.860	157

The average extinction coefficient for males is $1.296 = 16.92$ gm.; for females, $1.190 = 15.53$ gm.

It will be seen from Table 9 that from the ages of 16 to 60 inclusive the hemoglobin of the two sexes are in the ratio of 1.296 to 1.190; or, otherwise expressed, the female averages 91.8 of the value of the male. Expressed in absolute terms, the men average 16.92 gm., the women 15.53 gm.

TABLE 10.—INFLUENCE OF SEX ON HEMOGLOBIN FOR THE AGES, SIXTY-ONE TO SEVENTY YEARS

Age	Sum of Extinction Coefficients, Male	Number Cases	Sum of Extinction Coefficients, Female	Number Cases
61 to 65 years.....	18.919	15	19.254	16
66 to 70 years.....	21.089	17	17.821	15
	40.008	32	37.075	31

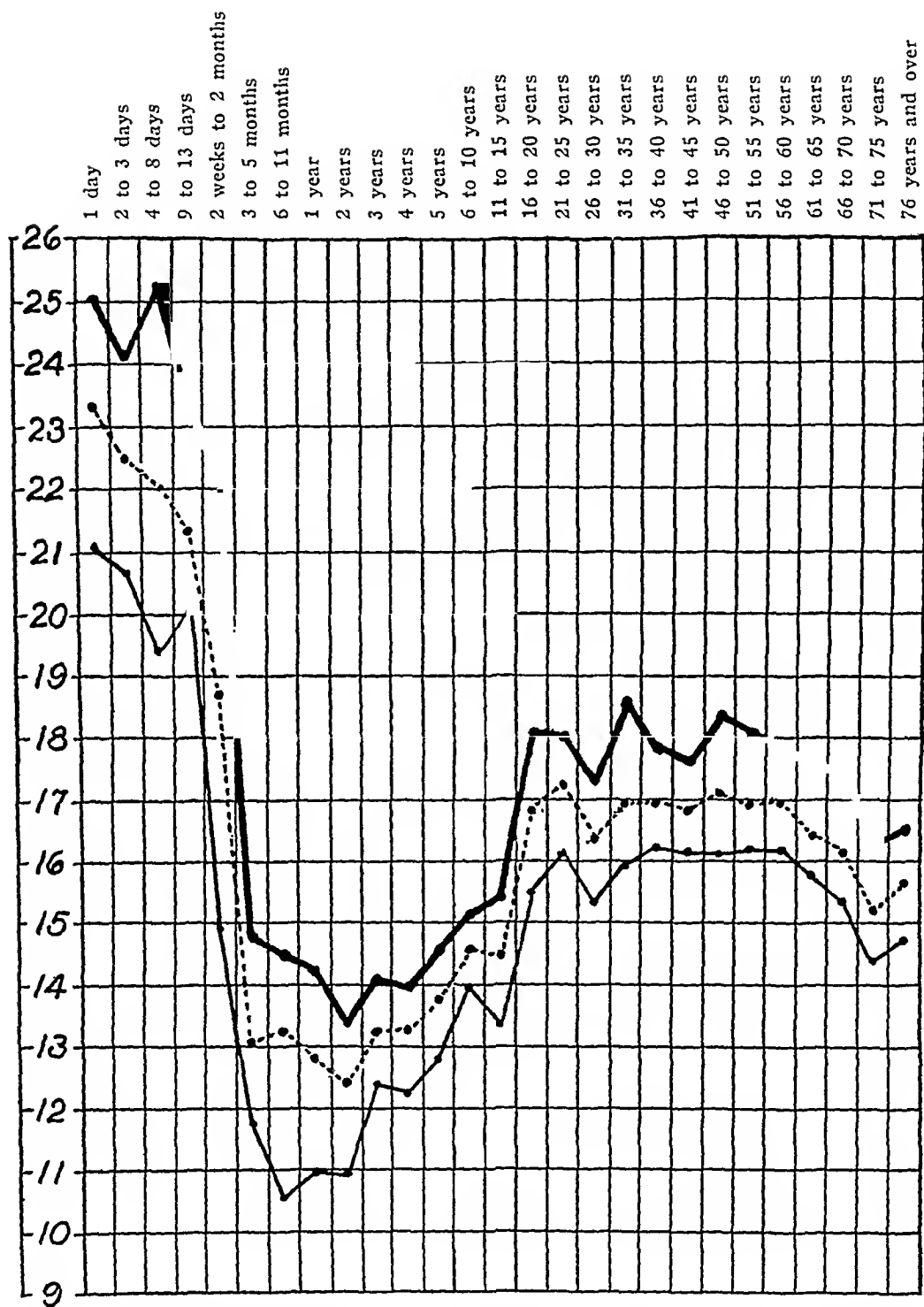


Fig. 3.—The average amount of hemoglobin, and the average amount for those having more than the average and also for those having less than the average, for males ranging in age from 1 day to over 76 years.

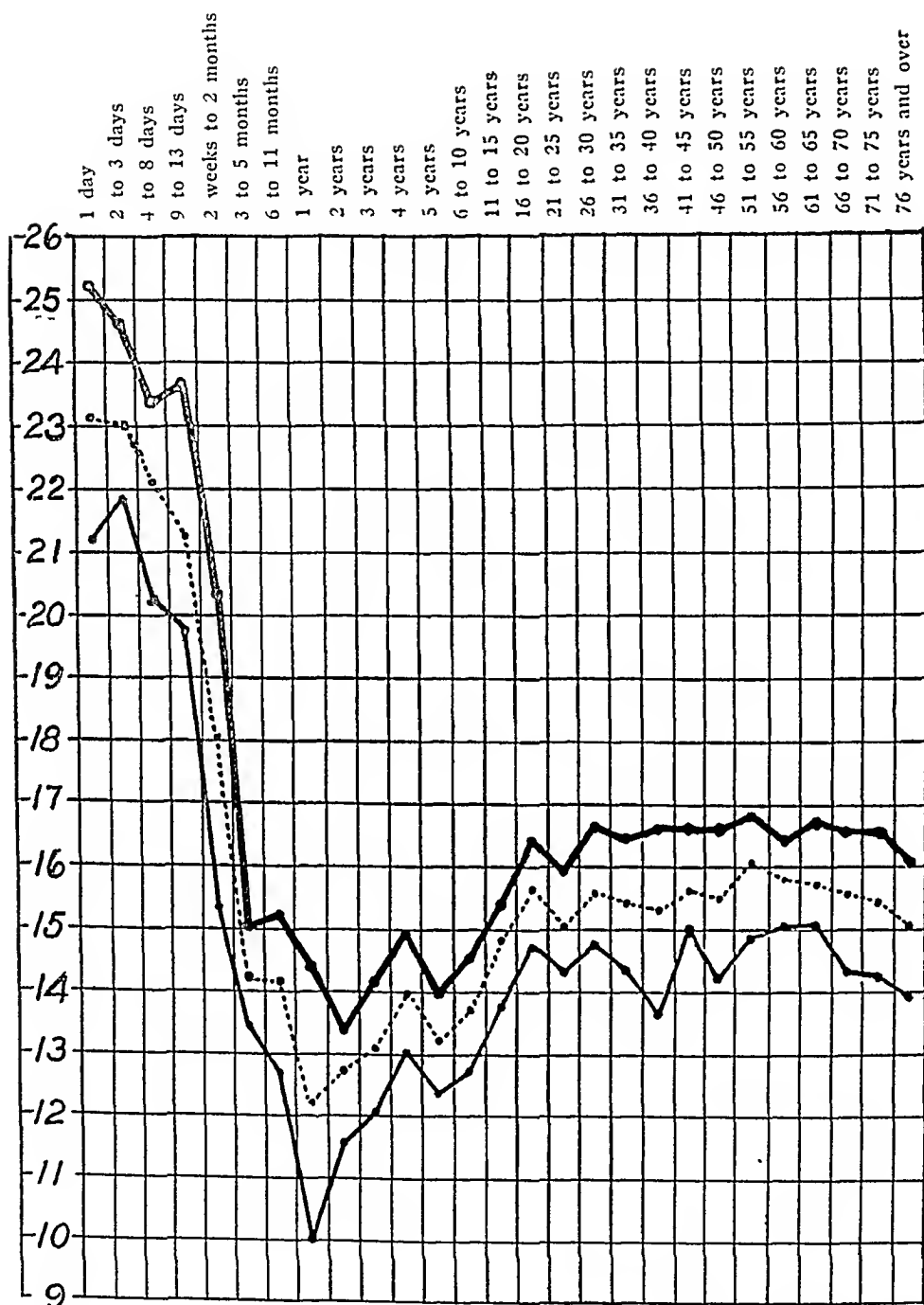


Fig. 4.—The average amount of hemoglobin, the average amount for those having more than the average and also for those having less than the average, for females varying in age from 1 day to over 76 years.

For the ages from 61 to 70 inclusive the values are as 1.250 to 1.196, that is, the value for the women is 95.6 per cent. of the value for the men. Expressed in absolute terms, the men average 16.32 gm., the women 15.61 gm.

TABLE 11.—INFLUENCE OF SEX ON HEMOGLOBIN FOR THE AGES ABOVE SEVENTY-ONE YEARS

Age	Sum of Extinction Coefficients, Male	Number Cases	Sum of Extinction Coefficients, Female	Number Cases
71 to 75 years.....	22.161	19	20.142	17
Over 76.....	36.010	30	26.495	23
	58.171	49	46.637	40

The averages are 1.187 for the men, and 1.166 for the women, or, expressed in absolute terms, 15.49 and 15.22 respectively.

It is, of course, quite desirable to know within what limits the hemoglobin values vary in individuals of the same age and sex. To obtain what might be properly regarded as an average variation we adopted the following method: We first averaged all of the values in a given group, then took all the values above this average, and averaged them separately, repeating the process with all the values below the average. This was done for male and female separately, and the results are shown in Figures 3 and 4.

An inspection of these figures shows that the variations from the average are somewhat greater in very early life. This is, of course, almost self-evident, when we realize how marked a difference in hemoglobin may be produced by a very slight difference in age during the early months of life. From the 3rd or 4th year onward this average variation is fairly constant, and amounts to approximately 1 gm. above or below the average norm.

CONCLUSIONS

From a simple inspection of the Figures the following conclusions are obvious:

1. The amount of hemoglobin in the blood of normal persons varies greatly at different ages, and follows a well-defined curve.
2. These age variations are so great that in determining whether a given blood contains more or less hemoglobin than normal, it is imperative to consider the age. These variations are greatest from birth to the 16th year.
3. Between the ages of 16 and 60 there is a marked difference between the two sexes, this difference growing less after the 60th year.

4. In view of these facts, it is evident that hemoglobinometers should be standardized in absolute terms, most conveniently in grams of hemoglobin per 100 c.c. of blood. (Because of the superior accuracy attained, it is highly desirable that the standardization of hemoglobinometers should be spectrophotometrically controlled.)

5. Whether or not a given blood contains a greater or less amount of hemoglobin than the normal can be determined only by a comparison of the absolute value obtained by a hemoglobinometer thus standardized, with the normal value for that age and sex, as shown by Table 7.

THE AUTOLYSIS OF NITROGENOUS COMPOUNDS OF THE BLOOD SERUM IN GENERAL PAR- ALYSIS AND DEMENTIA PRAECOX

WITH ITS BEARING ON THE ABDERHALDEN TEST *

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In previous communications¹ from this laboratory it was demonstrated that the blood serum from normal animals, treated according to the Abderhalden method, with substrates prepared from various tissues, gave positive reactions, thus proving that disease of the corresponding organs is not necessary for the occurrence of a positive Abderhalden reaction with such substrates. It was further shown that both with animal and human serums the appearance of a positive reaction varied with the thoroughness with which the substrates were washed with boiling water. All substrates used could, by repeated washing, be rendered incapable of producing positive Abderhalden tests. It was further established that the serum of persons suffering from general paralysis of the insane, when tested with brain substrate, showed a quantitatively different reaction from that of normal individuals. This difference, calculated by personal estimates of the degree of ninhydrin reaction, was illustrated by a curve which is here reproduced in Figure 1.

In order to establish this fact by quantitative methods we have performed a series of tests with brain substrates and the blood serums of normal persons, of patients presenting unmistakable evidence of general paralysis of the insane and others showing a dementia praecox type of reaction.

Estimations of the amount of amino-acid nitrogen were made, by the Van Slyke method, in the serum immediately after separation and again at the end of twenty-four hours, during which the samples were kept in a shaking machine at a temperature of 37 C. These samples included serum alone and serum mixed with 0.25 gm. of brain substrate. At the end of the period the serum was separated from the substrate by filtration. In Table 1 are given the figures thus obtained and the average results are shown in graphic form in Figure 2 for convenience of comparison with the results shown in Figure 1.

* Submitted for publication July 3, 1916.

* From the Laboratory of the Illinois State Psychopathic Institute.

* Read before the American Neurological Society, May 10, 1916.

1. Ross and Singer: THE ARCHIVES INT. MED., 1914, xiv, 552; Ibid., 1915, xv, 724.

These results seem to suggest very strongly that the coagulable nitrogen of the substrate can have nothing to do with the determination of a positive Abderhalden test, a conclusion which is strongly supported by the fact, previously published, that the materials removed from various organs by washing with slightly acidulated boiling water in the process of preparing the organs for substrates will themselves serve as efficient substrates for the production of a positive Abderhalden reaction.

TABLE 1.—INCREASE OF AMINO-ACID NITROGEN IN MILLIGRAMS PER CUBIC CENTIMETER OF BLOOD SERUM WHEN INCUBATED FOR TWENTY-FOUR HOURS AT 37 C.

	Donor of Serum	Before Incuba- tion	Increase After 24 Hours Without Substrate	Increase After 24 Hours with Brain Substrate Which Had Been Washed*			
				2 Times	4 Times	6 Times	11 Times
Normal.....	1	0.886	0.023	0.006	0.057	0.012	0.021
	2	0.604	0.009	0.111	0.033	0.020
	Average	0.745	0.016	0.103	0.057	0.025	0.021
General paralysis of the Insane	E. B.	0.520	0.001	0.163	0.028	0.023
	A. C.	0.796	0.005	0.073	0.059	0.012
	A. S.	0.732	0.018	0.116	0.046	0.001
	G. M.	0.597	0.007	0.220	0.188	0.099
	J. L.	0.399	0.026	0.192	0.122	0.110	0.085
	Average.....	0.609	0.012	0.154	0.122	0.087	0.045
Dementia praecox...	S. B.	0.604	0.019	0.186	0.060	0.041
	C. D.	0.684	0.020	0.154	0.028	0.028
	J. S.	0.815	0.014	0.074	0.052	0.030	0.000
	A. B.	0.794	0.010	0.074	0.037	0.004	0.000
	F. W.	0.596	0.019	0.126	0.056	0.040	0.045
	Average.....	0.699	0.016	0.123	0.048	0.033	0.023

* The water which had been used for the second and subsequent washings gave no reaction with ninhydrin.

Investigations were next undertaken of the antitryptic titer of serum, during which it was noted that the addition of placenta substrate to serum resulted in a considerable increase in the total nitrogen of the serum. It was found that this increase reached its maximum in about ten minutes. The substrate used was placenta which had been washed twice. The wash water was negative to ninhydrin and a negative result was obtained in the dialysate when this substrate was incubated with water or normal salt solution according to the Abderhalden technic.

To a number of tubes containing 0.25 gm. of this placenta were added 1 c.c. of blood serum. Of these tubes, one was immediately filtered after dilution to 20 c.c., a second was filtered at the end of ten minutes and the others after thirty, and 180 minutes respectively, the same dilution being made in each case. Kjeldahl determinations

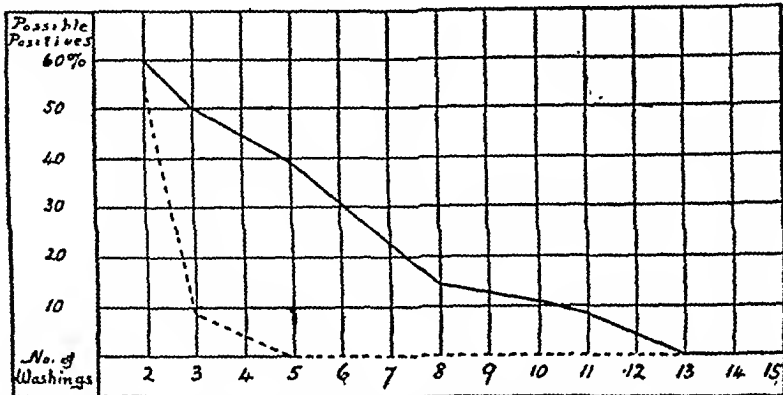


Fig. 1.—Proteolysis of brain substrate at different stages of washing by serum from normal persons and from patients with general paralysis. The solid line represents the results in general paralysis; the broken line, normal serum.

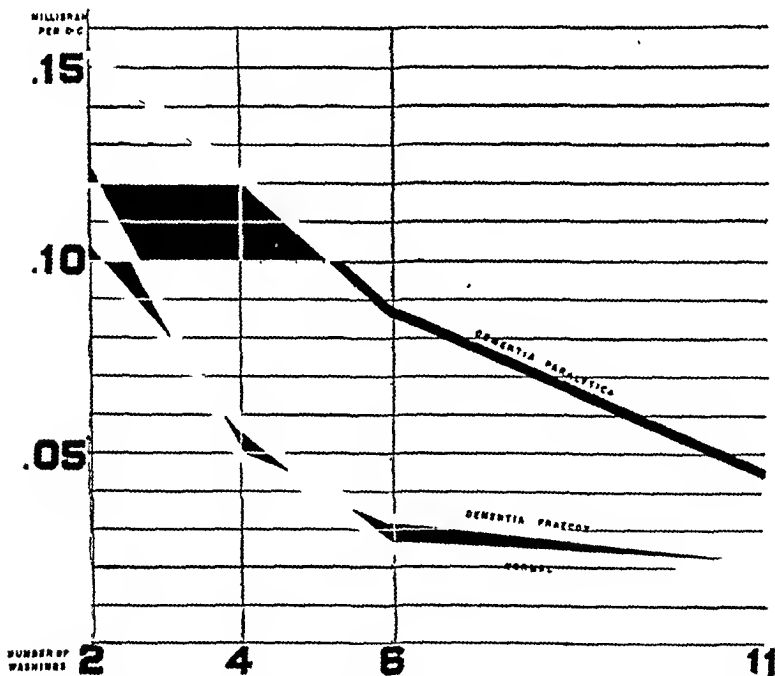


Fig. 2.—Increase of amino-acid nitrogen in serums incubated with brain substrate in various stages of washing.

were made on the blood serum alone, 0.25 gm. placenta alone, the filtrates from each of the above tubes and the residue with the filter paper in each instance. From these data it was possible to determine the increase in the total nitrogen of 1 c.c. of serum.

It was therefore decided to perform a series of tests on different blood serums and to compare the total autolysis of serum which had been treated for ten minutes with placenta substrate and then filtered with that which occurred in serum not so treated. The time allowed for the digestion was in all cases twenty-four hours and the method of determination used was that for noncoagulable nitrogen of Folin and Denis.² The total nitrogen of the serum was also determined by the Kjeldahl method. The results with normal, general paralytic and dementia praecox serums are given in Table 3.

TABLE 2.—INCREASE OF TOTAL NITROGEN OF SERUM FROM THE ADDITION OF PLACENTA SUBSTRATE

	Nitrogen, Mg.	Increase, Mg.
Original serum	11.653	
After momentary mixture with placenta.....	13.101	1.451
After 10 minute mixture with placenta.....	14.010	2.357
After 30 minute mixture with placenta.....	14.132	2.479
After 180 minute mixture with placenta.....	14.010	2.357

Figure 3 is a graphic representation of the average results for the three groups of blood serums given in Tables 1 and 3, those from the former being taken from the column for brain substrate which had been washed twice. The solid black represents the results from incubation of the serum alone, while the full height of the columns corresponds with those in serum which had been treated with substrate. It should be remembered in considering this chart that the first three columns refer to amino-acid nitrogen, the second three to total non-coagulable nitrogen and that the substrates used in the two sets were brain and placenta respectively.

In discussing these findings, one of the first points for especial emphasis is the fact that placental substrate allowed to act for only ten minutes is sufficient to remove antitryptic substances to such an extent that the increase in noncoagulable nitrogen during incubation for twenty-four hours exceeds that which occurs without the use of the substrate in serum from normal persons and from dementia praecox patients by approximately 260 per cent., and in general paralysis by 1,260 per cent. Furthermore, from the conditions of the experiment it is obvious that the nitrogen compounds which are split up must be those of the blood serum itself. The nitrogen derived from the substrate has, in each instance, been deducted from the figures here given for total noncoagulable nitrogen.

2. Jour. Biol Chem., 1911-1912, xi, 527.

The further observations, alluded to above, that the water which has been used for washing substrates contains materials capable of giving rise to positive Abderhalden tests and that substrates can be washed so thoroughly that they are no longer efficient, make it extremely probable that the active agent in removing antitryptic bodies from the serum is some soluble substance or substances. Necessarily,

TABLE 3.—INCREASE OF TOTAL NONCOAGULABLE NITROGEN IN MILLIGRAMS PER CUBIC CENTIMETER OF BLOOD SERUM WHEN INCUBATED FOR TWENTY-FOUR HOURS WITHOUT, AND AFTER, TREATMENT FOR TEN MINUTES WITH PLACENTA SUBSTRATE WHICH HAD BEEN WASHED TWICE, THE WASH WATER BEING NEGATIVE TO NINHYDRIN

	Donor of Serum	Total Nitrogen in Serum	Noncoagulable Nitrogen		
			Before Incubation	Increase after Twenty-Four Hours without Substrate	Increase after Twenty-Four Hours Subsequent to Treatment with Placenta for Ten Minutes Only
Normal.....	1	13.199	1.102	0.183	0.295
	2	14.793	0.938	0.069	0.332
	3	13.642	0.766	0.119	0.374
	4	13.465	0.903	0.154	0.333
Average.....	...	13.775	0.927	0.131	0.335
General paralysis of the insane	A. S.	11.288	1.346	0.000	0.197
	N. P.	12.667	1.047	0.071	0.392
	H. S.	13.376	1.065	0.003	0.448
	C. W.	13.908	0.964	0.011	0.265
	E. M.	14.137	1.033	0.043	0.340
Average.....	...	13.075	1.091	0.026	0.328
Dementia praecox.....	A. C.	15.375	1.152	0.032	0.076
	G. C.	14.174	0.975	0.244	0.634
	T. H.	14.035	0.898	0.064	0.292
	R. B.	14.571	0.970	0.174	0.325
Average.....	...	14.551	0.970	0.128	0.322

the concentration of these materials present in the wash water will vary according to the amount of water used in relation to the bulk of tissue being washed, the thoroughness of previous washings and the amount of these substances present in the tissue. The efficiency of the wash water will thus vary and we have found that it may be increased by careful evaporation. Some preliminary observations have been made with the wash water from placental tissue which seem sufficiently

significant to warrant mention here, although they are not by any means complete or exhaustive.

In one sample of such wash water it was found by the Kjeldahl method that nitrogen was present to the amount of 34.515 mg. per 100 c.c. Both urea and ammonium salts were present and determinations made of these two bodies gave 25.13 mg. urea nitrogen and 13.60 mg. ammonia nitrogen per 100 c.c., making a total of 38.73 mg. per 100 c.c., slightly larger than the Kjeldahl estimate for total nitrogen. It therefore seemed probable that the nitrogen present existed very largely in these two forms.

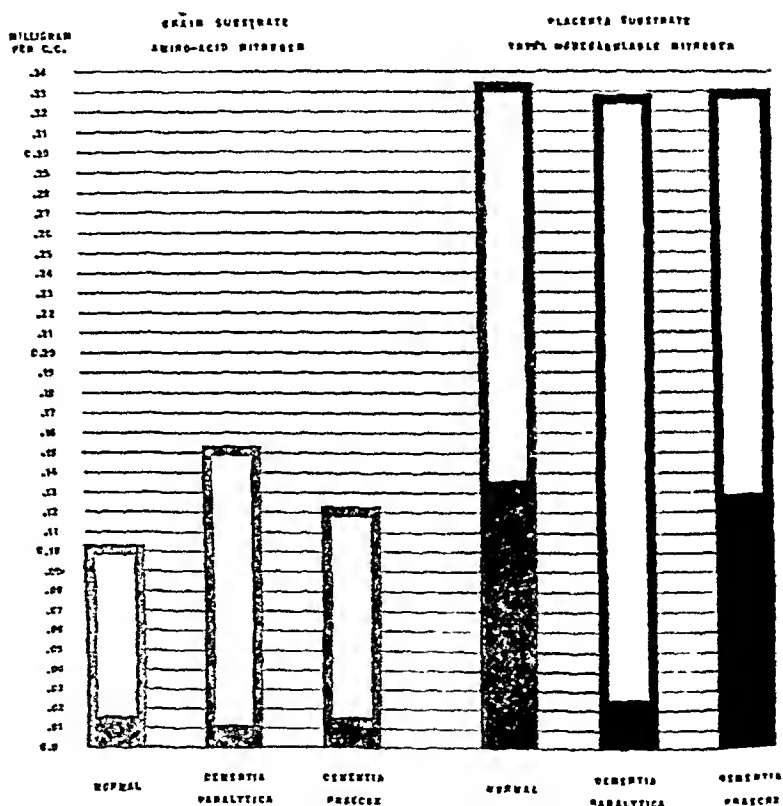


Fig. 3.—Effect of the removal of antitryptic substances from blood serums on the increase during incubation of amino-acid and of total noncoagulable nitrogen. Increases in the untreated serum are indicated in solid black, while those in the treated serum are represented by the full height of the columns.

Dialysis³ tests have been performed with blood serum mixed with placenta substrate, a solution of urea (1 c.c. contained 2.158 mg. of nitrogen), a solution of ammonium chlorid (1 c.c. contained 0.990 mg. of nitrogen) and a mixture of these last two. The tubes were

3. The dialyzing thimbles used were made of celloidin and we are not yet satisfied that they are free from objection.

incubated for sixteen hours and 10 c.c. of the dialysate tested with ninhydrin. The following results were obtained:

Serum alone	Negative
Serum with placenta	Positive
Serum with urea	Negative
Serum with ammonium chlorid	Positive
Serum with urea and ammonium chlorid.....	Positive

The positive reaction in each instance was faint and about equally so in all three. The serum used was that of a male general paralytic. It should be stated that in another test a positive was obtained with urea.

Attention may be called to certain other features in the tables and charts. The close similarity between dementia praecox and normal serum in all tests, with the wide divergence of that from general paralysis, is striking. Of course it is not possible to state without actual test that this is true for all substrates, but this seems at least probable if we are correct in regarding the substrate merely as a means of removing antitryptic properties.

It may be questioned, on the same grounds, whether we are justified in comparing the results of tests with placenta with those obtained when brain substrate is used. But it may be pointed out that the figures given offer a possible explanation for the fact that positive Abderhalden reactions are obtained with some serums and not with others. It will be observed that the ratio of the amino-acid nitrogen in the first set of tests to that of total noncoagulable nitrogen in the second set considered as 100 is as follows:

	Normal	General Paralysis	Dementia Praecox
Without substrate	13.0	46.0	12.5
With substrate	30.8	47.0	37.0

Amino-acid nitrogen gives a positive ninhydrin reaction; the lower products of lysis probably do not under the ordinary conditions of the Abderhalden test. Thus the blood serum of paretics not only has a higher antitryptic value, but, when this is neutralized or partly neutralized, the process of proteolysis takes place either less rapidly or less completely. The serum from dementia praecox also shows a somewhat greater proportion of amino-acid nitrogen and would therefore tend to develop a slightly larger percentage of positive Abderhalden reactions than the normal.

A comparison between the antitryptic titer of the different groups of serum, as measured by the two sets of tests, yields very strikingly similar results. The proportion of amino-acid nitrogen increase without substrate treatment to that with is 15.5 per cent. for the normal, 7.8 per cent. for general paralysis and 13 per cent. for dementia praecox. Corresponding figures for total noncoagulable nitrogen are 37.1

per cent., 20.3 per cent., and 38.5 per cent., respectively. If these are expressed in the form of ratios with general paralysis as 10, the results are as follows:

	Normal	General Paralysis	Dementia Praecox
Amino-acid nitrogen	20	10	17
Total noncoagulable nitrogen..	18	10	19

The number of cases examined is small and therefore broad conclusions are not advisable, but attention may be directed, in a further comparison of these three groups of serums, to the relation of non-coagulable nitrogen to total nitrogen. For both normals and dementia praecox it is 6.7 to 100 (although the figures are higher for dementia praecox), whereas in paresis this ratio is 8.4 to 100. Comparing the figures in Table 3 with those in Table 1, the percentage of noncoagulable nitrogen represented by amino-acid nitrogen, is as follows:

	Per Cent.
Normal	79.7
Dementia praecox	72
General paralysis	56

SUMMARY

1. The efficiency of brain substrate in destroying antitryptic bodies in blood serum, as estimated by determination of the amino-acid nitrogen produced, is gradually removed by repeated washing with boiling water.

2. Substrates prepared from placenta contain water-soluble substances capable of neutralizing antitryptic bodies. A sufficient amount of these substances can be extracted by the serum during ten minutes contact to permit free autolysis.

3. In the cases examined the average antitryptic titer of the blood serum was high for general paralysis and approximated the normal for dementia praecox.

4. After neutralization of antitryptic bodies the increase of non-coagulable nitrogen was approximately the same for normals, general paralytics and dementia praecox patients, but the proportion of amino-acid nitrogen was much greater in general paralysis and slightly greater in dementia praecox than in the normal.

5. The second wash water from placenta substrate contained urea and ammonium nitrogen, but was negative to ninhydrin. Positive Abderhalden tests have been obtained with ammonium chlorid as a substrate.

6. The noncoagulable nitrogen of the serum is increased by ten minutes' contact with placenta substrate.

CONCLUSIONS

Substrates neutralize antitryptic bodies in the blood serum, thus permitting fermentation of the nitrogenous constituents of the serum. This autolysis will, if not carried too far, cause a positive Abderhalden reaction.

The Abderhalden test is of no value as an index of disease or disorder of function in any particular organ.

AMMONIUM SALTS AND THE ABDERHALDEN TEST *

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In an earlier communication¹ we have shown that placental substrate, when extracted with water or normal salt solution, yielded considerable quantities of ammonia nitrogen, and that positive Abderhalden (ninhydrin) reactions had been obtained with blood serum dialyzed with ammonium chlorid as a substrate.

It has also been demonstrated² that, contrary to the opinion expressed by Abderhalden and others, all ammonium salts, if sufficiently concentrated, react positively to ninhydrin. None, with the exception of ammonium-sodium-hydrogen phosphate, gave a positive reaction in a dilution as great as 0.05 mg. nitrogen per cubic centi-

TABLE 1.—NINHYDRIN TESTS WITH AMMONIUM PHOSPHATE AND
GLUCOSE MIXTURE

Ammonia Nitrogen Content, Mg.	Glucose, Mg.	Result
0.28	2	Negative
0.35	2	+ (faint)
0.49	2	+
0.63	2	++
0.35	1	Negative
0.56	1	+ (faint)
0.70	1	+

meter, and the result here was so faint as to be negligible. It was, however, found that the addition of a reducing agent, pyridin, yielded positive reactions, even in such dilute solutions, with all ammonium salts. The method of conducting the ninhydrin test in these experiments differed from that of the Abderhalden technic in that 1 c.c. of 1 per cent. ninhydrin was used and the boiling was continued for twenty minutes.

In view of the fact that blood serum normally contains at least one reducing agent, glucose, in considerable quantity, it seemed worth while to perform tests with ammonium salts and glucose and to employ the technic of Abderhalden, wherein 0.2 c.c. of 1 per cent. ninhydrin is added to 10 c.c. and the mixture is boiled for one minute only.

* Submitted for publication July 25, 1916.

* From the Laboratory of the Illinois State Psychopathic Institute.

1. THE ARCHIVES INT. MED., p. 529.

2. Harding and Warneford: Jour. Biol. Chem., 1915, xxv, 319.

Qualitative tests of the normal salt extract from placenta substrate demonstrated the presence of considerable amounts of phosphoric acid and, since ammonium phosphate seemed to react especially readily with ninhydrin, it was decided to employ the neutral ammonium phosphate for this purpose. As a reducing agent we have used glucose. Table 1 gives the results of a series of tests in each of which the volume of ammonium phosphate-glucose solution was made up to 10 c.c.

Placenta substrate, which had been washed twice (the wash water was negative to ninhydrin), was extracted with normal salt solution for sixteen hours. The ammonia nitrogen in the extract was estimated as 0.62 mg. for each gram of placenta. Table 2 gives the results of boiling portions of the extract, made up in each case to 10 c.c. by the addition of water, with and without glucose, for 1 minute with 0.2 c.c. of 1 per cent. ninhydrin:

TABLE 2.—NINHYDRIN TESTS WITH NORMAL SALT EXTRACT OF PLACENTA SUBSTRATE AND GLUCOSE MIXTURE

Ammonia Nitrogen Content, Mg.	Equivalent Placenta Substrate, Gm.	Glucose, Mg.	Result
0.99	1.6	...	Negative
0.62	1	1	Doubtful
0.73	1.2	1	+

In the Abderhalden tests, as usually carried out, the substrate is washed four or five times before use and the amount of ammonia nitrogen which would be extracted in sixteen hours would be considerably less than with the substrate here employed, which had been washed with boiling water only twice. The weight of substrate used is generally from 0.25 to 0.5 gm. Furthermore, glucose is present in normal blood serum to the extent of about 1 mg. per cubic centimeter. From 1 to 1.5 c.c. are used for a test and the serum dialyzed into 20 c.c. of water, 10 c.c. of which are used for the actual ninhydrin reaction. This 10 c.c. can therefore rarely contain more than 0.5 mg. glucose.

In the results given above it was necessary to use the extract from 1.2 gm. placenta substrate with 1 mg. glucose in order to obtain a positive ninhydrin reaction following the Abderhalden technic, and there would therefore appear to be but little danger of error from this source, provided care is used in washing the substrate and too large quantities of serum and substrate are avoided.

In order to confirm this opinion we have carried out some dialysis tests with placenta substrate and a solution of glucose and others with blood serum and ammonium phosphate solution. In the former 0.5, 1, and 1.5 gm. placenta were placed in dialyzing thimbles with, in each instance, 1 c.c. of glucose solution containing 2 mg. glucose. There

were placed 20 c.c. distilled water in the tube outside the thimble and 10 c.c. of this was used after sixteen hours' incubation for the ninhydrin test. All gave a negative result.

In the second series blood serum from a normal person was used, some being drawn before breakfast and a second sample one hour after breakfast. The glucose content was determined by the method of Strouse, Stein and Wiseley³ to be 0.725 mg. per cubic centimeter before breakfast, and 1.189 mg. per cubic centimeter after breakfast. The results of dialysis tests were as given in Table 3.

TABLE 3.—NINHYDRIN TESTS WITH THE DIALYSATE FROM AMMONIUM PHOSPHATE AND BLOOD SERUM MIXTURE

	Serum, C.c.	Ammonium Phosphate in Mg. of Ammonia N	Result
Before breakfast.....	1.5	0.315	+ (very faint)
	1.5	0.49	+
	1.5	0.7	+
After breakfast.....	1.5	0.315	Lost
	1.5	0.49	+ (very faint)
	1.5	0.7	+ (slight)

The reaction with 0.7 mg. ammonium phosphate and serum taken before breakfast was very marked, more so than that with the same amount and after-breakfast serum. Since the latter contained a larger quantity of glucose, it seems probable that the positive reactions here depend on autolysis of serum and are not merely reactions between the ammonium salt and ninhydrin in the presence of a reducing agent, the glucose of the serum. This reaction is similar to that previously reported with ammonium chlorid as a substrate.

SUMMARY AND CONCLUSIONS

Ammonium phosphate will serve as an efficient substrate in the performance of the Abderhalden test.

Ammonium phosphate in dilute solution will give a positive reaction with ninhydrin, used according to the Abderhalden technic, in the presence of glucose.

Although ammonia nitrogen and phosphoric acid are present in the watery extract from placental substrate and glucose is present in the blood serum, the quantities are too small to give rise to error when the Abderhalden technic is followed.

3. Strouse, Stein and Wiseley: Bull. Johns Hopkins Hosp., 1915, xxvi, 211.

HEMATOCHYLURIA

OBSERVATIONS ON THE FAT CONTENT OF THE URINE AND THE PATHOLOGY OF THE CONDITION *

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The following case on the medical service of Dr. Henry A. Christian at the Peter Bent Brigham Hospital gave an opportunity for the study of hematochyluria with especial reference to the fat content of the urine.

S. G. (P. B. B. H. Med. No. 1636), a man, aged 27 years, single, West Indian mulatto, a seaman, entered the Peter Bent Brigham Hospital, Sept. 14, 1914, complaining of disturbance of micturition and peculiarly colored urine. The family history was negative. The patient was born in Barbados, where he lived until 15 years of age. He had always been in good health. No history of urinary disturbances prior to the present illness was obtained. In 1903, two years after leaving Barbados, he noticed slight enlargement of the left testicle. Five years before entrance he had gonorrhea, which was not followed by any complications.

Three years previous to admission, while urinating, the flow suddenly stopped and the patient had to be catheterized. This attack was followed by pain and tenderness in the region of the symphysis pubis. He noticed at that time that the urine was very dark. One year previous to admission the left testicle became markedly swollen, but was not painful or tender. During the last nine months previous to admission there were four attacks of acute retention similar to the one described. During one of these attacks, one week previous to admission, he noticed for the first time that the urine was almost milk white with a reddish tinge. The urine has remained of this color. Aside from the attacks, he felt quite well, except for weakness. He lost 20 pounds in weight in the six months previous to entrance.

Physical examination showed a well-developed, but rather poorly nourished, young mulatto lying quietly in bed in no evident distress. The pupils were regular, equal and reacted normally to light and accommodation. There was some pyorrhea alveolaris, and the upper and lower central incisors were carious. The throat was negative. There was no enlargement of the lymph nodes, except at the angle of the right jaw. The chest and lungs were negative. Both heart sounds were heard and were normal; there was reduplication of the second sound at the base. The pulse was of good quality, regular and normal. The systolic blood pressure was 120 mm. of mercury, the diastolic 70 mm. The abdomen was negative; the spleen was not felt; the liver was not enlarged; there were no masses in the abdomen and no tenderness. In the right groin there was a scar about 3 cm. in length, the result of trauma. The left half of the scrotum was somewhat enlarged and felt like a varicocele. The left testicle was somewhat enlarged, but was not tender. The right testicle was normal. The superficial and deep reflexes were present and normal. Rectal examination was negative.

* Submitted for publication July 3, 1916.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

* This study was done under a grant from the Proctor Fund of the Medical School of Harvard University for the Study of Chronic Diseases.

On admission the urine was reddish brown and turbid. The odor was distinctly less urinous than normally. After sedimentation the supernatant fluid was distinctly milky. It was acid, with a specific gravity of 1.020, albumin 0.2 per cent, and no sugar. The sediment showed an occasional leukocyte, many red blood cells, and occasional hyaline and coarsely granular casts. Under the oil immersion lens were seen myriads of minute, highly refractile droplets, which stained with Sudan III. The sediment of many of the specimens contained numerous small blood clots. Repeated examination of these failed to reveal any filarial embryos. On standing, many of the specimens coagulated in about fifteen minutes into firm, gelatinous masses. These dissolved in about two and one-half hours. There then formed a narrow, bright red zone consisting of red blood cells, above this a broad, pinkish white zone and on top a narrow, milky zone.

Blood examination revealed red blood cells 3,160,000, white blood cells 7,200, hemoglobin (Sahli) 77 per cent.; the differential count showed polymorphonuclear neutrophils 53 per cent., eosinophils 25 per cent., basophils none, large mononuclear cells 10 per cent., small mononuclear cells 12 per cent. The erythrocytes showed a moderate achromia. Repeated examinations of the blood at night and in the day failed to show any embryos of filaria. Ten c.c. of blood examined for parasites by the method of Staubli yielded negative findings.

The stools showed numerous rhabditiform embryos of *Strongyloides stercoralis*, otherwise they were not abnormal. The Wassermann reaction on the blood serum was positive. The von Pirquet cutaneous test with tuberculin was negative. Analysis of the gastric contents, bismuth Roentgen-ray examination of the gastro-intestinal tract and electrocardiographic studies of the heart yielded normal findings. The temperature was irregularly remittent, reaching 103 on one occasion, and falling to normal before discharge.

A cystoscopic examination, made by Dr. Goetsch, showed the bladder mucosa definitely reddened with a considerable amount of surface desquamation. The ureteral orifices were of normal appearance. From the left orifice were seen frequent spurts of turbid urine, which momentarily obscured the view in that locality. From the right orifice no such turbid urine was seen. The ureters were then catheterized; there was a good flow of almost clear urine from the right side; from the left side the flow was about half as rapid as from the right and the urine was opalescent, definitely turbid and blood tinged.

The urine varied much in gross appearance; many of the specimens were free from blood and others were quite clear. No periodicity was observable in either of these characteristics. During his stay in the hospital his weight varied between 51 and 47.8 kg. and his hemoglobin fell 22 per cent. Three weeks after admission he had an attack of acute retention, the only one while in the hospital. He was not catheterized and about fifteen minutes later he voided a small amount of very bloody urine containing several fibrinous clots. He was given 0.3 gm. of salvarsan intravenously on October 31. The specimen voided after this contained much less blood and fat than usual. From this time until the date of discharge, November 13, the urine remained free of fat and blood and entirely normal in appearance.

THE FAT CONTENT OF THE URINE

The quantity of fat in chylous urines has been reported several times; the determinations have, however, usually been made on single specimens and without regard to the amount of fat ingested. Dunn¹ reports a case of filarial chyluria in which the determination was made

1. Dunn: Tr. Col. Phys. and Surg., Phila., 1898, xx, 80.

on a single voiding. This contained 2.2 per cent. fat. Young² reports two cases in which the fat content of the urine was 1.8 per cent. and 2.6 per cent. Salkowski³ studied a case and found the urine to contain 0.4 per cent. of fat. Henson⁴ has made observations in a case of lymphscrotum on the relation of the fat content of the diet to the amount in the effusion.

The question naturally arises, is the chylous fluid mixed with the urine true chyle or lymph? The composition of lymph is extremely variable, as shown by analyses cited by Hammarsten⁵ made on lymph from a fistula in the thigh. This lymph contained 47 parts of fat per 1,000 after the subject had partaken of fat; while on a starvation diet the content varied between 0.6 and 2.6 parts per 1,000. Low⁶ reports a case with "chylous" turbid urine in which the urine contained no fat. He therefore introduced the term "lymphuria" to distinguish cases with turbid fat-free urine containing lymph from true cases of chyluria, and believes the pathology of the two conditions to have certain differences. These will be discussed later.

The method in the present case was to collect a sample of each voiding. Of this, 10 c.c. were mixed with about an equal amount of sand and evaporated to dryness on the water bath. The sand containing the urinary residue was then collected in filter papers and extracted with ether for twelve hours in a Soxhlet fat extractor. The ether extract was then transferred to a weighed dish and the ether evaporated by a current of air until the dish had assumed a constant weight. From the amount found in this way the amount of ether-soluble fat in the total specimen of urine was calculated. Table 1 shows the percentage content of fat in the specimens of urine.

On admission the patient was put on the regular house diet, the fat content of which is variable and not accurately known. During this period, which extended from September 14 to September 29, the fat content of single specimens was between 0.2 and 1.2 per cent.

On September 29 he was placed on a fat-poor diet, fat content averaging 13.7 gm. per day. The single voidings during this period, which extended to October 6, averaged 0.35 per cent. fat, and the total average daily output of fat was 3.4457 gm. The daily total fat in the urine in relation to fat intake is shown in Figure 1.

When the house diet was resumed the amount of fat in the single specimens showed marked increase, rising to between 1 and 1.4 per cent. The effect of the transition from house diet to fat-poor diet

2. Young: *Jour. Trop. Med. and Hyg.*, 1914, xvii, 2.

3. Salkowski: *Berl. klin. Wchnschr.*, 1907, xlv, 51.

4. Hensen: *Arch. f. d. ges. Physiol.*, 1875, x, 94.

5. Hammarsten: *Text-Book Physiol. Chem.*, New York, Ed. 5, 1910, p. 252.

6. Low: *Jour. Lond. Sch. Trop. Med.*, 1912, 1, 243.

FAT CONTENT OF URINE IN CASE OF HEMATOCHYLURIA

Date	Time of Voiding	Fat, %	Date	Time of Voiding	Fat, %
Sept. 14.....	4:00 p. m.	0.962		4:00 a. m.	0.482
	6:40 p. m.	0.404		9:00 a. m.	1.251
	9:20 p. m.	1.124		11:00 a. m.	0.506
Sept. 15.....	1:00 a. m.	0.124		2:30 p. m.	1.022
	5:15 a. m.	0.402		4:00 p. m.	0.426
	9:15 a. m.	0.562		5:45 p. m.	0.320
	12:45 p. m.	0.540		10:00 p. m.	0.436
	4:50 p. m.	0.192	Oct. 9.....	2:00 a. m.	0.366
	10:30 p. m.	0.401		4:00 a. m.	0.340
Sept. 16.....	6:00 a. m.	0.340		7:40 a. m.	0.686
	12:00 noon	0.452		2:45 p. m.	0.864
	8:00 p. m.	0.213		4:00 p. m.	0.380
	10:15 p. m.	0.382	Oct. 10.....	10:20 a. m.	0.754
Sept. 18.....	4:00 a. m.	0.223		11:00 a. m.	0.730
	6:30 a. m.	0.852		12:30 p. m.	0.624
	12:50 p. m.	0.103		5:00 p. m.	0.782
	2:20 p. m.	0.482		9:45 p. m.	0.648
	3:00 p. m.	0.529	Oct. 11.....	1:45 a. m.	0.386
	6:00 p. m.	0.925		9:30 a. m.	0.863
Sept. 19.....	1:00 a. m.	0.437		12:00 p. m.	0.704
	8:30 a. m.	1.110		1:35 p. m.	0.986
	1:00 p. m.	1.282		3:00 p. m.	0.742
	7:30 p. m.	0.550		4:45 p. m.	0.622
Sept. 20.....	3:00 a. m.	0.649		6:00 p. m.	1.060
	7:30 a. m.	0.710	Oct. 12.....	2:15 a. m.	0.384
	12:00 noon	1.217		4:00 a. m.	0.320
	2:00 p. m.	1.167		10:00 a. m.	0.976
	4:20 p. m.	0.747	Oct. 13.....	10:00 a. m.	0.850
Sept. 21.....	8:00 a. m.	0.472		11:30 a. m.	0.682
	12:00 noon	0.547		12:45 p. m.	0.950
Sept. 22.....	3:00 a. m.	0.500	Oct. 14.....	4:00 a. m.	0.446
	8:30 p. m.	0.610		6:30 a. m.	0.376
Sept. 23.....	1:00 a. m.	0.617		11:20 a. m.	1.381
	6:00 a. m.	0.582		11:40 a. m.	0.741
	11:25 a. m.	0.462		3:10 p. m.	0.864
	2:30 p. m.	0.550		9:20 p. m.	0.446
	8:00 p. m.	0.623	Oct. 15.....	4:00 a. m.	0.360
Sept. 24.....	5:00 a. m.	0.410		9:15 a. m.	1.061
	11:30 a. m.	0.392		12:50 p. m.	1.204
	4:00 p. m.	0.426		3:45 p. m.	0.861
	8:00 p. m.	0.561		6:20 p. m.	0.799
	11:00 p. m.	0.378		9:00 p. m.	1.627
Sept. 25.....	2:00 a. m.	0.403	Oct. 17.....	3:30 a. m.	0.750
	10:00 a. m.	0.801		4:45 p. m.	0.940
	12:00 a. m.	0.675		6:30 p. m.	0.898
	3:15 p. m.	0.706		11:30 p. m.	1.151
	6:10 p. m.	0.458	Oct. 18.....	4:00 a. m.	0.838
Sept. 26.....	1:00 a. m.	0.456		10:45 a. m.	1.202
	2:00 a. m.	0.495		2:40 p. m.	1.550
	3:30 a. m.	0.561	Oct. 19.....	4:00 a. m.	0.759
	8:30 a. m.	0.840		7:15 a. m.	1.181
	9:20 a. m.	0.661		12:00 noon	1.291
	12:30 p. m.	0.919		1:00 p. m.	1.442
	3:30 p. m.	1.122		8:30 p. m.	0.788
	9:50 p. m.	0.389	Oct. 20.....	4:00 a. m.	1.061
Sept. 27.....	4:00 a. m.	0.218		10:00 a. m.	0.986
	9:45 a. m.	0.967		12:35 p. m.	0.686
	1:00 p. m.	1.673		9:50 p. m.	1.101
	8:00 p. m.	0.989	Oct. 21.....	2:00 a. m.	0.506
Sept. 28.....	2:00 a. m.	0.810		8:00 a. m.	1.202
	4:50 a. m.	0.590		3:20 p. m.	1.102
	9:30 a. m.	0.786	Oct. 22.....	2:00 a. m.	1.204
	12:40 p. m.	0.869		6:00 p. m.	1.308
	3:00 p. m.	1.013	Oct. 23.....	9:10 a. m.	1.011
Sept. 29.....	6:00 p. m.	1.611		10:30 p. m.	0.986
	2:45 a. m.	0.704		3:00 p. m.	0.704
	4:40 a. m.	0.898	Oct. 24.....	8:00 a. m.	0.986
	10:40 a. m.	1.342		11:00 a. m.	0.630
	3:00 p. m.	0.365		11:40 a. m.	0.580
	3:40 p. m.	0.306		2:15 p. m.	0.986
Sept. 30.....	8:40 p. m.	0.422		4:00 p. m.	0.543
	1:45 a. m.	0.256		6:00 p. m.	1.104
	4:25 a. m.	0.144	Oct. 25.....	4:00 a. m.	0.462
	8:45 a. m.	0.234		2:15 p. m.	1.702
	11:30 a. m.	0.212		5:00 p. m.	0.408
	12:00 noon	0.254		11:00 p. m.	0.804
	3:30 p. m.	0.352	Oct. 26.....	6:45 a. m.	0.386
	5:30 p. m.	0.295		9:40 a. m.	0.860
	7:40 p. m.	0.462		11:30 a. m.	0.582
	10:40 p. m.	0.412		1:20 p. m.	0.940

FAT CONTENT OF URINE IN CASE OF HEMATOCHYLURIA—(Continued)

Date	Time of Voiding	Fat, %	Date	Time of Voiding	Fat, %
Oct. 1.....	1:00 a. m.	0.356		2:35 p. m.	0.406
	4:00 a. m.	0.234		6:00 p. m.	1.023
	8:05 a. m.	0.538		8:20 p. m.	0.742
	10:30 a. m.	0.426	Oct. 27.....	5:00 a. m.	0.420
	2:15 p. m.	0.469		7:00 p. m.	0.923
	3:15 p. m.	0.340	Oct. 28.....	4:45 a. m.	0.436
	4:33 p. m.	0.286		1:55 p. m.	0.906
	9:30 p. m.	0.450		2:25 p. m.	0.604
Oct. 2.....	5:30 a. m.	0.380		11:30 p. m.	0.486
	12:00 noon	0.320	Oct. 29.....	2:00 a. m.	0.789
	2:30 p. m.	0.452		11:00 a. m.	0.920
	7:00 p. m.	0.522		4:30 p. m.	0.969
Oct. 5.....	4:00 a. m.	0.282		8:25 p. m.	1.128
	11:00 a. m.	0.342	Oct. 30.....	8:30 a. m.	0.729
	1:00 p. m.	0.424		3:30 p. m.	0.001
	8:20 p. m.	0.402	Oct. 31.....	1:45 a. m.	0.719
Oct. 6.....	2:00 a. m.	0.262		2:00 p. m.	0.121
	2:00 p. m.	1.207	Nov. 1.....	5:00 a. m.	0.098
	6:00 p. m.	1.402		8:00 a. m.	0.006
	10:45 p. m.	0.346		9:00 p. m.	0.003
Oct. 7.....	4:00 a. m.	0.572	Nov. 2.....	4:00 a. m.	None
	9:30 a. m.	0.856		9:00 a. m.	None
	1:00 p. m.	1.401		7:00 p. m.	None
	7:10 p. m.	0.600		10:00 p. m.	None
Oct. 8.....	2:30 a. m.	0.421			

and vice versa on the percentage of fat in single voidings of urine is shown in Figure 2.

The diet next used was one calculated to contain protein 150 gm., carbohydrate 300 gm., and fat 80 gm. Actual estimation of the fat showed this to be 78.5 gm. The amount of fat in the food refused each day was calculated and this subtracted from 78.5 gave the amount actually ingested, as shown in Figure 3. It will be seen from this illustration that the amount of fat in the urine is not strictly proportional to the amount in the food, that is, variations in the intake do not cause proportional variations in the output. During this period, October 15 to 31, the average daily intake was 66.39 gm. and the average daily output was 6.451 gm. The average content of single voidings was 0.9 per cent.

A consideration of these figures would seem to indicate that there are other determining factors besides the amount of fat in the food; for when the amount of fat ingested was increased almost five times, that is, from 13.7 gm. to 66.39 gm., the amount in the urine was not quite doubled, 3.445 gm. to 6.451 gm. per day. Part of this discrepancy might result from faulty absorption when taking a fat-rich food.

In this particular case there was no observable difference between the night and day specimens as regards fat content, that is, the position of the body did not seem to be a factor. Charteris,⁷ however, records a case in which chyluria could be induced at will by giving the patient milk to drink, and causing him to remain supine for a short while. The condition was of at least ten years' duration.

7. Charteris: *Lancet*, London, 1911, ii, 1011.

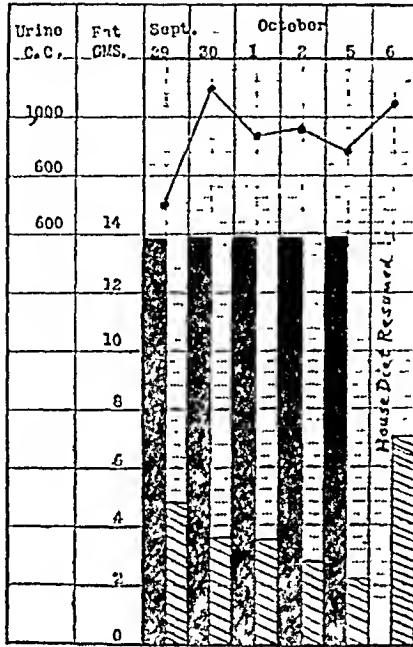


Fig. 1.—The total daily amount of fat in the urine while on a diet low in fat. Solid black columns indicate approximate daily fat intake; cross-hatched columns indicate daily fat output in the urine. Dots joined by line indicate daily amount of urine.

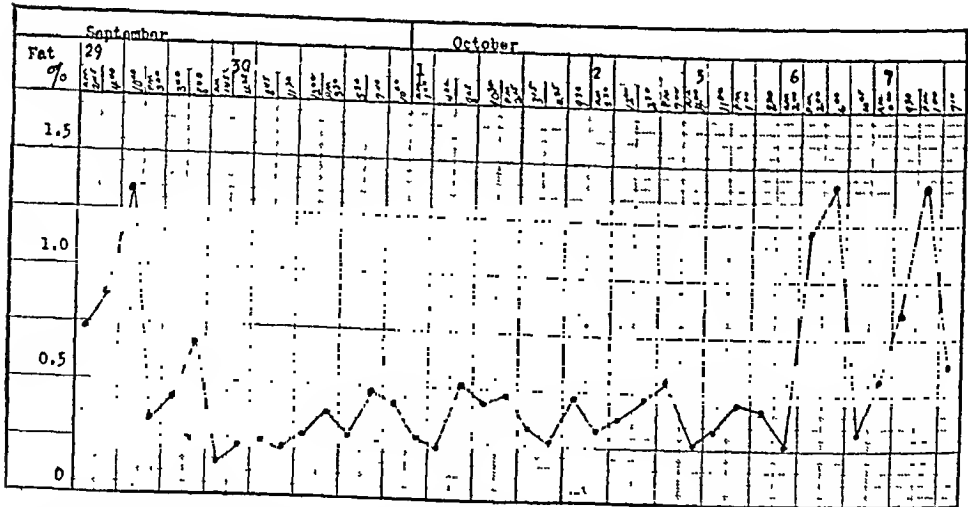


Fig. 2.—The changes in percentage of urinary fat in single voidings on transition to and from a fat-poor diet. The dots represent the percentage of fat in single voidings. On September 29 a diet low in fat was begun and on October 6 it was discontinued for a diet fairly rich in fat.

The daily fluctuations of chyluria and clear urine observed in some cases are explained by Magnus-Levy⁷ on a mechanical basis. In about a third of the cases cited by him the urine was turbid for the greater part of the day, and in the majority of the remainder only at night, or when the patient was in a reclining posture. A few patients presented chyluria only when in the upright position. These variations have been explained by assuming that the valves in the lymphatics are

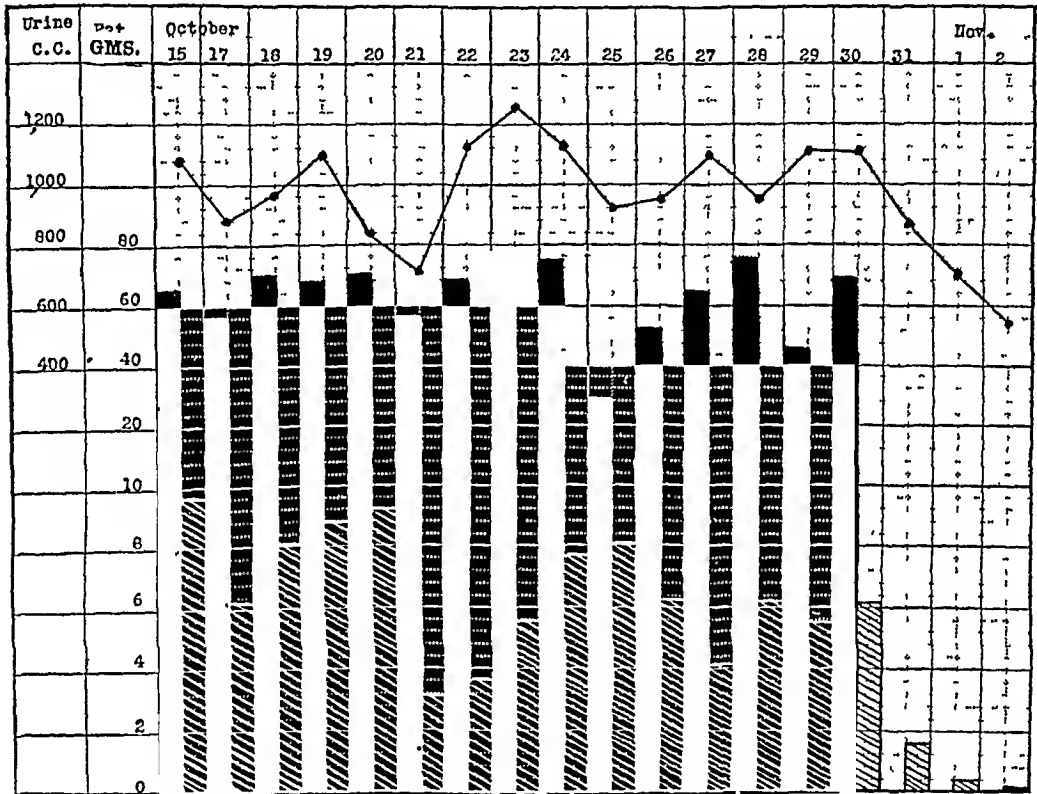


Fig. 3.—The relation of the total daily urinary fat to the amount ingested while on a diet relatively high in fat. Solid black columns indicate approximate daily fat intake; cross-hatched columns indicate daily fat output in the urine. Dots joined by line indicate daily amount of urine.

insufficient, when the body is in a certain position, so that the communication between the lymphatic varix and the urinary system is patent. Other factors which suggest themselves, but have not, I think, been demonstrated in their exact relation to the degree of chyluria, are the size of the fistula into the urinary tract, the hydrostatic pressure causing the emptying of the lymph into the urinary system, and the damming back of the chyle from the thoracic duct.

8. Magnus-Levy: *Ztschr. f. klin. Med.*, 1908, lxxvi, 482.

PATHOLOGY

Opportunities to study the pathology of chyluria have not been numerous. As long ago as 1862 Carter⁹ suggested that the condition was due to the rupture of a varicose lymphatic vessel into the bladder. That this is a cause is shown by the case reported by Havelburg.¹⁰ The patient had had chyluria for six months, and filaria had been found in the blood and urine. Necropsy revealed a large tumor, extending from the left kidney to the bladder. It consisted of many loculi and its contents were chylous. The upper and left walls of the bladder were in intimate contact with the tumor. On opening the bladder there was found a fistulous opening from which chylous fluid could be squeezed.

Confirmatory of this view is the case of a Japanese who consulted Pope¹¹ because of turbid urine. On cystoscopic examination a fistula large enough to admit a ureteral catheter was seen near the base of the trigonum, discharging chylous urine. Further examination showed that the urine did contain fat. No filaria were found and there was a history of probable psoas abscess in infancy, which, it was thought, might have been the causative factor.

That the above condition is not essential to the production of chyluria and is, indeed, absent in the majority of instances is shown by several cases which may be cited in some detail.

In the well-known case of MacKenzie¹² the whole of the space between the kidneys was occupied by a mass of varicose lymphatics, which extended down to the iliac vessels. The receptaculum chyli began in two large lymph sinuses about the size of a pencil, one from each side of the aorta. Near the aortic opening in the diaphragm it was joined by a third large lymphatic sinus. The thoracic duct was sinuous and much pouched for three or four inches, varying in diameter from $\frac{3}{8}$ to $\frac{1}{2}$ inch, pervious part of the way, filled above with a loose clot. At its termination it passed through a mass of lymphatic tissue, was pervious and about the size of a crow's quill. Although the varix closely embraced the urinary tract, no fistulous communication was observed. Finding the kidney greatly dilated, MacKenzie thought it probable that within the kidney between the lymphatic and urinary apparatus there was a communication by which chylous lymph entered the urine. The bladder appeared to be normal. Chyle and lymph had, however, entirely disappeared from the urine three months before death.

9. Carter: *Med.-Chir. Tr.*, London, 1862, xlv, 189.

10. Havelburg: *Arch. f. path. Anat.*, 1882, lxxxix, 365.

11. Pope: *California State Jour. Med.*, 1909, vii, 285.

12. MacKenzie: *Tr. Path. Soc.*, London, 1882, xxxiii, 394.

Manson¹³ records the postmortem findings in a case of filarial chyluria. The thoracic duct commenced below in an ill-defined tumor, situated in front of the vertebrae and below the diaphragm; the thoracic duct was enlarged throughout, though variously, its diameter being equal to the little finger below and to a goose quill above. The upper two or three inches of the duct, with its venous outlet, were quite occluded, below this the duct was patent and its lumen was occupied throughout its length by a firm thrombus, which in its upper extent was closely and almost structurally connected with the duct, but below, where the latter was wider, it was loose and easily detachable. The mass in which the thoracic duct commenced extended downward as far as the right iliac fossa and closely embraced one of the ureters. The kidneys, ureters and bladder were found to be quite healthy and no communication whatever could be found between them and the tumor. The latter on section was tough and fibrous and showed here and there gaping vessels with the walls cut across, which were probably dilated lymphatics.

Low⁶ reports a case in which the pathologic findings were quite different from those described above. In his case the thoracic duct was entirely normal, as was also the receptaculum chyli. The kidneys were somewhat enlarged and on section exuded hemolymph. The lymphatics of the kidneys and pelves were in a varicose condition. In a lymphatic of the pelvis of the kidney a calcified filaria was found surrounded by dense fibrous tissue. The left ureter with its lymphatics was uniformly dilated and thickened. No cause of obstruction was found. The bladder was distended, hypertrophic, and contained hemolymph and clots. From its wall there were villus-like projections of varicose lymphatics. Low is of the opinion that in his case there was a leakage of lymph from the left kidney, left ureter, the bladder and probably from the right kidney, in which the condition was less marked. This wide distribution indicated an extensive disturbance or blockage of the lymphatic stream going to the thoracic duct. No obstruction was found, but the conclusion was arrived at that filariae act as an intense irritant producing fibrosis and consequent obstruction. The urine in this case though turbid was free from fat and led to the introduction of the term "lymphuria." The pathologic explanation of this, Low thinks, lies in the fact that in this case obstruction was below the thoracic duct, that is, in the efferent renal lymphatics. For chyle to reach the lymphatics around the bladder there must be regurgitation in the thoracic duct and such regurgitation could not take place if the duct and its venous outlet were patent.

That extensive fibrosis in the region of the hilus of each kidney might produce obstruction is evident when it is recalled that there are

13. Manson: Davidson's Hygiene and Diseases of Warm Climates, p. 814.

normally only four to seven efferent lymphatic trunks which leave the hilus and run along with the renal artery and vein, according to Poirier and Cuneo,¹⁴ to end principally in the juxta-aortic glands of the corresponding side and accessorially in the preaortic glands. After passing through these series of glands the efferents of the right side pass through the right pillar of the diaphragm and terminate in the thoracic duct. On the left side the efferents pass through the left pillar of the diaphragm and also join the thoracic duct. Obstruction of the terminal trunks would lead to gradual dilatation and eventual rupture. That chyluria is not more frequent in cases of lymphatic varix with partial obstruction seems to indicate that the anastomoses are ordinarily sufficient to drain the chyle away from the urinary tract.

SUMMARY

In a patient with chyluria the fat content of the urine varied markedly with the fat content of ingested food. On a fat-poor diet it averaged 0.35 per cent. and on the house diet it rose to from 1 to 1.4 per cent. With diet containing a daily average of 66.39 gm. of fat the average daily output of fat in the urine was 6.45 gm. The amount of fat in the urine, however, did not increase in direct proportion to the amount of ingested fat. In some cases chyle escapes directly into the bladder or ureter through a fistulous opening; in other cases the chyle finds its way into the urine within the kidney. In some cases the fluid entering the bladder is true chyle, in others it is lymph.

14. Poirier and Cuneo: *Treat. Human Anat., The Lymphatics*, Leaf's Translation.

METABOLISM STUDIES OF ANGIONEUROTIC EDEMA *

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INTRODUCTION

The subject of this investigation is a woman suffering at irregular intervals from attacks of transient edema, sometimes with convulsions, and with a persistent but variable eosinophilia. She has been under observation, more or less constantly, in the wards of the university hospital for a period of eight years and has been during that time the subject of many detailed studies, planned with the object of throwing some light on the etiology or exact nature of her condition. These, however, have yielded no specific information and the condition remains diagnosed only as an obscure type of angioneurotic edema. The present studies are an attempt to demonstrate any changes which may have occurred concomitantly with the attacks of edema, and include a determination of nitrogen utilization; an estimation of the acid-base relations of the body fluids; a study of the chlorid excretion; and uncompleted desultory studies of calcium and fat metabolism and of respiratory exchange.

CLINICAL NOTES

The patient, a woman, now 54 years of age, married and without children, was admitted to a medical ward of the hospital on the service of Dr. Alfred Stengel on June 27, 1908, in a state of unconsciousness following her first convulsion. She had, however, been having monthly attacks of swelling about the eyes from February of the preceding year. The menses had stopped in September of that year.

Since June, 1908, she has had convulsions and edematous attacks at irregular intervals and has spent the greater part of each year in the hospital. She is not confined to bed except during and for a few days following her more severe attacks. Sometimes an attack consists of a single brief convulsion and again of a number coming on without warning and in rapid succession, the type of the convulsion being clonic and involving first the face and then the body generally. Edema of the circumocular areas, the arms, the chin, and the anterior neck frequently precedes, accompanies, or immediately follows these seizures, but either the edema or the convulsions may occur independently. A typical attack of edema appears at first as a slight puffiness about the eyes or a little firmness of the inner aspects of the upper forearms. These parts are often quite itchy and there are sometimes associated urticarial manifestations elsewhere. In the course of a few days the swellings reach their height and then gradually subside. At their height an increase in the circumference of the arm above and below the elbow of from 2 to 4 cm. has often been demonstrated. At

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* From the John Herr Musser Department of Research Medicine of the University of Pennsylvania, Philadelphia.

such times also there is an increase in the patient's weight of from 4 to 8 pounds. One attack may immediately follow another, but as a rule there is an interval of several weeks.

The urine constantly shows a trace of albumin and a few hyaline and granular casts. Its amount is decreased before an attack of marked swelling, and subsequently rises after the cessation of the attack. In an interval between attacks the phenolsulphonephthalein elimination in two hours after intravenous injection was 50 per cent.; during an attack it was 35 per cent. The urea of the blood equals 28 mg. in 100 c.c. of blood. The leukocyte count of the blood varies between normal and 44,000. An eosinophilia is always present, the percentage varying from 27 to 85. Numerous blood pressure studies show that there is a lowering of the readings with the onset of the swellings and that convulsions are most likely to occur during this depression. The systolic pressure varies from 115 to 187 mm. of mercury and the diastolic from 65 to 85. Wassermann tests were twice negative. Repeated examinations of the feces for intestinal parasites have yielded no information.

METHODS

The patient was under observation in a metabolic ward of the hospital during these studies, the details of her diet and the collection of her excreta being supervised by a nurse whose duties were confined to metabolism cases. The diet varied in the several periods of our study, and in the intervals she was permitted the full ward diet. In Periods 1, 3, and 4 the Folin diet¹ was used; in Period 2 a diet of carbohydrates and fats with a minimal amount of protein was employed. In Periods 5 and 6, respectively, a salt free and a high salt diet were given. The urine was collected under toluol and at the end of each 24 hours transferred from the ice box of the ward to that of the laboratory. The feces were marked off into periods by means of carmine.

The total nitrogen of the urine and of the food and feces was estimated by the Kjeldahl-Gunning method. Ammonia was determined by the Folin method and sodium chlorid by the technic of Volhard-Arnold. The determinations of the total acidity of the urine were made by the method of Palmer and Henderson.²

RESULTS AND COMMENT

The Nitrogen Metabolism.—In the periods in which the total nitrogen metabolism was studied (Table 1) the Folin diet was employed because it has been standardized and comparisons of results can therefore be made with known figures. It will be observed that in each period there is a positive nitrogen balance. This nitrogen retention, while never very marked, is greater in the two periods which include attacks of edema (Periods 1 and 4a) than in the two normal

1. Folin, O.: Approximately Complete Analyses of Thirty "Normal" Urines, *Am. Jour. Physiol.*, 1905, xiii, 45.

2. Henderson, L. J., and Palmer, W. W.: On the Several Factors of Acid Excretion, *Jour. Biol. Chem.*, 1914, vii, 305.

TABLE 1.—METABOLISM IN ANGIONEUROTIC EDEMA

Period	Date	Nitro- gen In- take, Gm.	Urine						Feces, Nitro- gen, Gm.	Nitro- gen Balance	Clinical Notes
			Vol- ume, C.c.	Total Nitro- gen, Gm.	Am- monia, Gm.	NH ₃ in N/10 Acid	Acid- ity in N/10 Alk.	NH ₃ plus Acid- ity			
1	1915 10/ 1	17.39	1,950	14.96	0.39	1.76	+0.67	Marked edema
	10/ 2	17.42	1,460	14.14	0.32	1.76	+1.52	
	10/ 3	17.39	1,240	14.63	0.49	1.76	+1.00	
	10/ 4	17.31	1,560	14.90	0.62	1.76	+0.65	
	10/ 5	17.04	1,375	14.19	0.62	1.76	+1.09	
	10/ 6	18.02	1,760	14.31	0.66	1.76	+1.95	
	10/ 7	18.39	1,725	13.49	0.66	1.76	+3.14	
	10/ 8	17.07	1,640	13.49	0.54	1.76	+1.82	
	Average	17.50	1,588	14.26	0.54	1.76	+1.48	
2a	12/ 8	15.75	2,600	10.54	0.41	249	364	613	0.93	+4.28	Convulsion, no edema
	12/ 9	0	860	8.49	0.33	200	260	460	0.93	-9.43	
	12/10	16.67	710	10.39	0.41	252	330	582	0.94	+5.35	
	12/11	17.12	1,240	15.78	0.62	376	480	856	0.94	+0.40	
	Average	12.38	1,352	11.30	0.44	269	358	628	0.93	+0.15	
2b	12/12	17.20	1,630	14.44	0.53	320	510	830	1.32	+1.44	Normal period
	12/13	18.60	1,700	16.05	0.53	320	510	830	1.32	+1.23	
	12/14	17.70	1,890	16.65	0.62	376	560	936	1.33	-0.28	
	12/15	16.90	1,730	16.43	0.53	332	500	832	1.32	-0.85	
	Average	17.60	1,737	15.89	0.55	337	520	857	1.32	+0.38	
4a	1916 1/27	17.2	1,040	13.06	0.59	360	460	820	1.59	+2.55	Marked edema
	1/28	17.8	1,330	13.60	0.63	384	460	844	1.60	+2.60	
	1/29	17.3	1,480	14.23	0.68	412	500	912	1.59	+1.48	
	1/30	17.7	2,335	14.28	0.63	385	487	872	1.60	+1.82	
	1/31	14.5	1,500	14.20	0.60	364	500	864	1.60	-1.30	
	2/ 1	17.4	1,430	13.49	0.54	328	490	818	1.60	+2.31	
	Average	17	1,519	13.81	0.61	372	483	854	1.60	+1.58	
4b	2/ 4	17.3	2,175	16.32	0.61	370	575	945	1.26	-0.28	Normal period
	2/ 5	18.5	1,625	16.24	0.56	340	550	890	1.26	+1.00	
	2/ 6	18.2	1,450	15.12	0.56	340	500	840	1.27	+1.81	
	2/ 7	18.3	1,770	16.32	0.67	412	530	942	1.27	+0.71	
	Average	18.1	1,775	16	0.60	365	539	904	1.26	+0.81	

periods (3b and 4b). In the period which includes a convulsion (3a) the nitrogen retention is a little less even than for the two normal periods. It would appear, therefore, that a convulsive seizure does not interfere with the utilization of nitrogen, whereas an edematous attack does to a limited extent.

The Acid and Ammonia Excretion.—The daily estimations of the total acidity of the urine in the normal periods (3b and 4b) are quite similar. For the intermediate period, which included a marked attack of edema, the figures are only slightly lower. It would seem that this decrease is too slight to be considered of importance in relation to the reaction of the body fluids. Furthermore, this decrease in the acid output of Period 4a is associated with a slightly greater ammonia excretion than occurs in the normal periods. It is the sum of these two factors that represents the efficiency of the kidney in retaining alkali and we must look, therefore, to this figure for any influence on the reaction of the body fluids. In order to express these two factors in the same units the amount of the ammonia excretion is expressed in the number of cubic centimeters of tenth-normal acid necessary to neutralize it, as well as in the usual way, just as the total acidity is expressed in the number of cubic centimeters of tenth-normal alkali necessary to neutralize it. The sum of the two is presented in a separate column, and it will be noted that the variation between the figures for the normal periods and for the period of edema are negligible. In Period 3a, during which there was no edema, but in which a convulsive seizure occurred, there is some reduction in the total acidity, but on the day of the convulsion no food was taken, and consequently the figures are misleading.

The Chlorid Excretion.—Table 2 shows in a number of attacks a clear-cut fall in the sodium chlorid excretion during the several days preceding and including the development of edema. In each instance on the day of the most marked edema the chlorid figures were rising and subsequently they were above normal. In Periods 1, 3, and 4 the salt intake was constant and the relatively low excretion figures for the several days preceding the height of the edema therefore indicate clearly a retention of chlorids. This is further emphasized by the large amounts of chlorid excreted during the periods of subsidence of the edema.

In Period 2, although the amount of intake was not definitely controlled, the diet was sufficiently constant, as indicated by daily determinations of the urinary nitrogen, to exclude the possibility that irregularity in diet could account for the marked diminution in the sodium chlorid excreted on the four days previous to the height of the edema. In Period 5 the patient was on a salt-free diet, and although a convulsion with a little edema did occur, the latter was practically

TABLE 2.—CHLORID EXCRETION DURING ATTACKS OF ANGIONEUROTIC EDEMA

	Period 1, Folin Diet			Period 2, Low Protein Diet			Period 3, Folin Diet			Period 4, Folin Diet			Period 5, Salt-Free Diet			Period 6, High-Salt Diet		
	Date	Urine, Vol., C.c.	Urine NaCl, Gm.	Date	Urine, Vol., C.c.	Urine NaCl, Gm.	Date	Urine, Vol., C.c.	Urine NaCl, Gm.	Date	Urine, Vol., C.c.	Urine NaCl, Gm.	Date	Urine, Vol., C.c.	Urine NaCl, Gm.	Date	Urine, Vol., C.c.	Urine NaCl, Gm.
No edema...	1915 10/ 1	1,950	9.2	1915 11/ 3	1,400	5.2	1915	1916 1/24	1,740	9.6	1916	1916
	10/ 2	1,460	7.2	11/ 4	1,080	3.6	1/25	1,320	6.6
	10/ 3	1,240	6.8	11/ 5	1,020	2.0	1/26	1,025	6.6
Edema developing..	10/ 4	1,560	8.4	11/ 6	1,200	2	12/ 4	760	3.6	1/27	1,040	7.2	3/21	850	2.3
	10/ 5	1,375	8	11/ 7	1,390	3	12/ 5	1,160	7.6	1/28	1,330	9.6	3/22	1,225	1.4	4/26	540	9
Edema at height.....	10/ 6	1,760	10	11/ 8	1,030	5.6	12/ 6	1,500	10.6	1/29	1,480	9.8	3/23*	1,280	1.6	4/27†	870	14.5
Edema subsiding.....	10/ 7	1,725	10.4	11/ 9	1,375	8.2	12/ 7	2,700	19.4	1/30	2,335	14	3/24	390	1	4/28	960	14.4
	10/ 8	1,640	10.	11/10	1,520	9.4	12/ 8	2,600	14.3	1/31	1,500	11.4	3/25	770	0.7	4/29	1,030	18

* Convulsion; edema extremely slight.

† Convulsion; edema very marked.

negligible. The patient was on this diet for a number of weeks and at no time did any appreciable swelling develop, although convulsions did occur. In Period 6 she was put on a high salt diet (the usual hospital diet with 10 gm. of salt added) and a convulsion occurred and associated with it was a marked edema. Unfortunately the figures which we present include but one day before this period of pronounced swelling; the excretion for that day, however, shows a preliminary retention.

Other Data.—In addition to the results presented in our tables we have made some investigations of the calcium and fat metabolism, but these studies have not been sufficiently completed to justify their publication. We may state, however, that they point toward normal fat and calcium utilization. Also some investigations of the carbon dioxide content of the blood and the alveolar air and of the chlorid content of the blood plasma have been made for us in this patient and found normal.

CONCLUSIONS

There is some evidence, as is indicated in our clinical notes, of an impaired renal function in this patient, and it is impossible to say to what extent this disturbance may have influenced our results. We feel justified, nevertheless, in presenting the following conclusions:

1. The attacks of swelling in an individual with an obscure type of angioneurotic edema are associated with a retention of nitrogen, which is greater than appears in intervening periods.

2. The excretion of acid bodies, so far as it can be determined by estimations of the total acidity and ammonia excretion in the urine, is not altered during these attacks.

3. A disturbance of the sodium chlorid metabolism is evidenced by a reduced elimination during the three or four days preceding the maximum swelling and by a corresponding excess of excretion afterward.

4. The convulsions from which the patient suffers are not associated with a nitrogen balance which is significantly different from that of normal periods, and there is no coincident change in the acid, ammonia, or sodium chlorid excretion.

5. A low chlorid intake appears to have a beneficial effect on the attacks of edema, but does not influence the convulsions.

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THE ACTION OF THE SO-CALLED FEMALE REMEDIES ON THE EXCISED UTERUS OF THE GUINEA-PIG *

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Introduction: The present paper is an introduction to a study of the so-called female remedies, drugs which have had more or less extensive clinical use, but which have not been subjects of thorough pharmacologic or clinical study. Judging from the large number of preparations of a proprietary or "patent" nature containing one or more of these drugs that are on the market at present, we must regard them as still extensively used. The purpose of the investigation was to determine whether any of the group possessed actions that could be referred to the uterus.

In this paper are presented their actions or lack of action on strips of the excised uterus of the guinea-pig. The method has certain limitations. A few experiments on strips of intestine indicate that the action is in no manner specific to the uterus. It seems safe to conclude, however, that if there is a positive action on the excised uterus, whether stimulation or depression, that a similar action would be exhibited on the uterus in situ if the drug reached the organ in a like concentration; such experiments on the uterus in situ are contemplated. In the text certain conclusions are drawn relative to the concentration of the drugs used in this work and the possibility of like concentrations being obtained in the body.

It may not be amiss to state at this place, that while a large number of the drugs studied exert definite actions on strips of the isolated

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* From the Pharmacologic Laboratories of the University of Nebraska, College of Medicine, Omaha, and Western Reserve University, Cleveland.

* This investigation was undertaken at the suggestion of the Therapeutic Research Committee of the American Medical Association and the Association assumed part of the expense of the investigation.

uterus, it is highly improbable that the concentrations necessary to elicit the action could be introduced into the body.

Methods: The usual methods were followed. A longitudinal strip of the uterus of the guinea-pig was attached to a muscle lever and immersed in a bath (50 c.c.) of Tyrode's fluid, kept well oxygenated by a constant stream of oxygen. The bath was kept at a fairly uniform temperature, about 38 C., although occasional variations did not seem to influence the action. The movements of the lever were recorded on a revolving drum. Usually there was a latent period of about twenty or thirty minutes before the regular contractions were initiated; sometimes the latent period was shorter and often much longer. Six experiments were usually carried on at the same time, strips from the same



Fig. 1.—*Aletris farinosa* (unicorn root); Experiment 65b; the evaporated fluidextract to make a 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds.

uterus being used. Frequently all strips from a given uterus failed to contract; again one strip failed to contract and others contracted well. In the later stages of pregnancy, when there is a larger amount of tissue, parts of the uterus were occasionally kept on ice over night and used on the next day, and rarely on the third day. As others have found, the pregnant uterus, especially in the later stages, usually contracts more vigorously than the virgin uterus and there are fewer inactive uteri in the pregnant group; for this reason the pregnant organ was usually employed. The action of a given drug sometimes presented differences between the virgin and the pregnant uterus; these differ-

ences will be discussed under the individual drugs. After obtaining a satisfactory control tracing of the normal contraction, the drug was added to the bath and the tracing continued for about fifteen minutes before transferring to fresh stock solution; occasionally the drug was allowed to act for a much longer period.

Preparations of the Drugs Used:¹ The fluidextract, the evaporated fluidextract and the infusion were employed. The fluidextract was used in the larger number of experiments, for the results with it did not differ materially from those with the evaporated extract. The fluidextracts used contained from 40 to 60 per cent. alcohol. Control experiments, with percentages of alcohol about the same as the fluidextracts made in the bath, were practically without action on the strips of the uterus; nevertheless, a large number of control experiments were made with the evaporated fluidextracts of most of the drugs and with but few exceptions, to be discussed under the individual drugs, the results did not differ materially from those of the fluidextract. Further, all but three of the fluidextracts (*Chamaelirium luteum*, *Leonurus cardiaca* and *Dioscorea villosa*) precipitated when added to the bath, and as many of the precipitates were very heavy, it was thought that a more intimate mixture would occur if the fluidextracts were added directly to the bath. When evaporated, the fluidextract was not exposed to a temperature higher than from 50 to 60 C.

Concentration of the Drugs Used: It was aimed to use a concentration of the drug that would approximate, therapeutically, the concentration in the blood under the most favorable conditions. If we assume that the average dose of the fluidextracts (2 c.c.) be absorbed promptly and equally distributed throughout the tissues of the body, the concentration in an adult (60 kg.) would be about 1 to 30,000; if all of the drug remained in the blood, a phenomenon, of course, that is inconceivable, the concentration would be about 1 to 2,000. The majority of the experiments were made with a much higher concentration than this (1 to 1,000); in other words, the concentrations used were greater than the highest conceivable concentration that could be

1. All the preparations used were furnished by the American Medical Association chemical laboratory. The crude drugs were identified and found true to name as follows: by Prof. Henry Kraemer: *Aletris farinosa*, *Caulophyllum thalictroides*, *Cypripedium pubescens*, *Dioscorea villosa*, *Ichthyomethia piscipula*, *Leonurus cardiaca*, *Mitchella repens*, *Passiflora incarnata*, *Pulsatilla pratensis*, *Scrophularia nodosa* (marylandica), *Scutellaria lateriflora*, *Senecio aureus*, *Valeriana officinalis*, *Chamaelirium luteum* and *Acer spicatum*; by Prof. E. N. Gathercoal: *Viburnum opulus*, *Viburnum prunifolium* and *Cnicus benedictus*. One each of the following fluidextracts was made by L. E. Warren of the American Medical Association chemical laboratory from the authentic drugs: *Acer spicatum*, *Viburnum prunifolium*, *Viburnum opulus* and the bark of the stem of the *Viburnum prunifolium*; all other fluidextracts were made by different firms and their identities were not established, but as the actions of two preparations of each drug were similar, their identity is probably authentic.

obtained therapeutically. As there were many exceptions to the average result, this strength was increased to 1 to 500 with some of the drugs without altering the type of action; occasionally more dilute solutions were effective. The strips were placed in fresh Tyrode solution before the addition of a different drug.

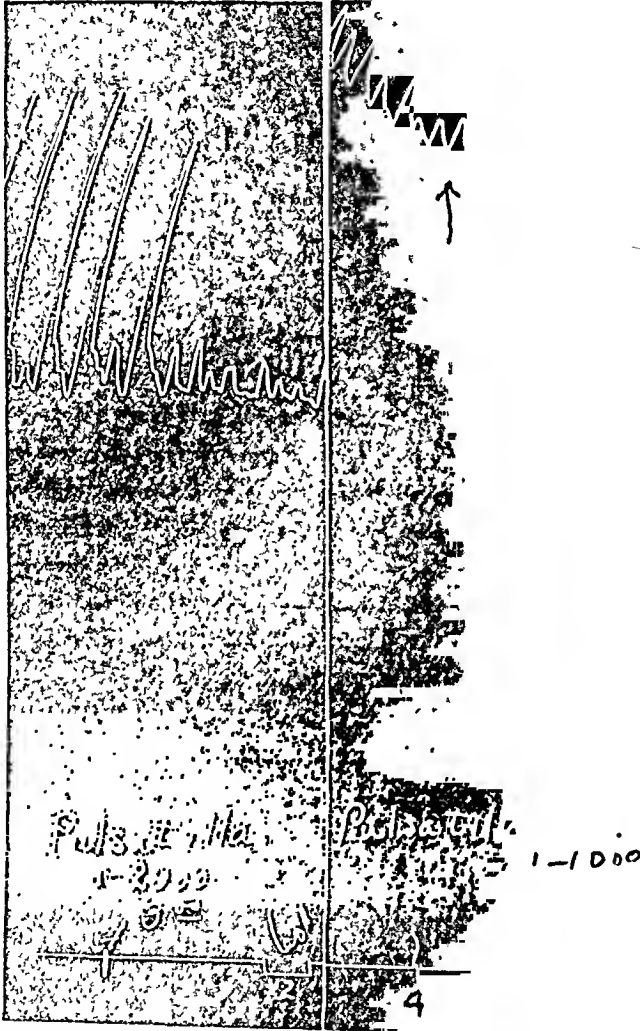


Fig. 2.—*Pulsatilla pratensis* (pulsatilla); Experiment 91c, late pregnancy; the fluidextract to make a 1 to 2,000 solution was added at "1"; contractions were not resumed and when placed in a fresh bath the strip went into a state of very great tone, and pulsatilla, 1 to 1,000 at "4" again caused cessation of the contractions. The tracing is interrupted between "2" and "4."

The Phenomena to Be Discussed: The action of the drugs was examined as affecting the rate and amplitude of excursion and the state of the muscular tone, these being considered the factors that determine the stimulant, depressant or negative action of the drugs. The rate may be considered an indication of the muscular irritability; the excursion, of the expulsive or parturient efficiency, and the tone as

an indication of the postpartum, styptic and, together with the excursion, of the abortifacient efficiency of a drug. The term "rate" always refers to the number of contractions per unit of time, and not to the duration of the individual contraction. The degree of relaxation of the strip was taken as the indication of the muscular tone. There is a close interrelation between rate, amplitude and tone. Under average conditions an increased rate usually prevents complete relaxation, so that apparently the muscular tone of the strip is increased. In such

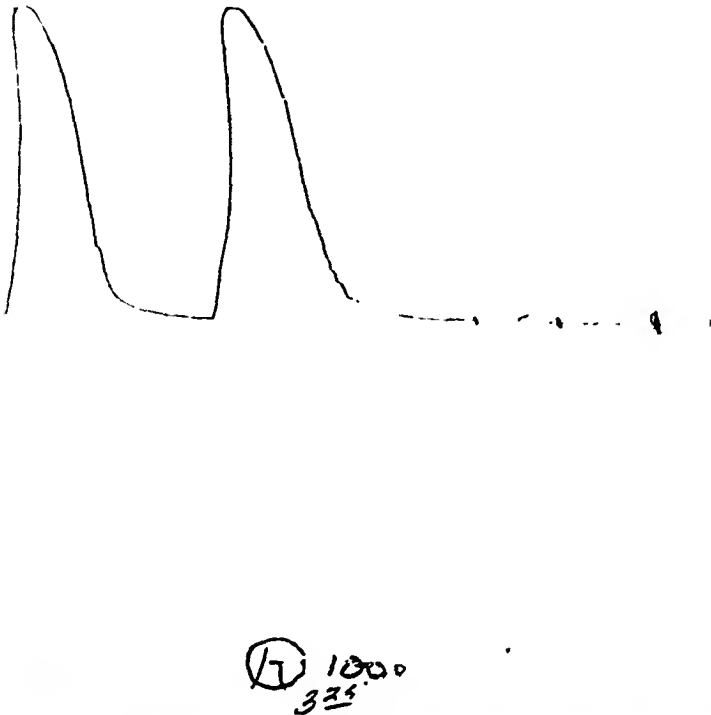


Fig. 3.—*Ichthyomethia piscipula* (Jamaica dogwood); Experiment 98d, late pregnancy; the fluidextract was added at "1" to make a 1 to 1,000 solution.

cases, however, there may be no actual increase of the tonicity of the muscular substance. Occasionally there was either an increase or decrease of tone with little or no change in rate or amplitude of the contractions. This would indicate a direct action on the muscular tone. In vigorously contracting uteri the rate is usually infrequent, so that there is plenty of time for complete relaxation. Under such conditions there may be considerable variation in the rate and amplitude without variation in the tone; this is especially true in advanced

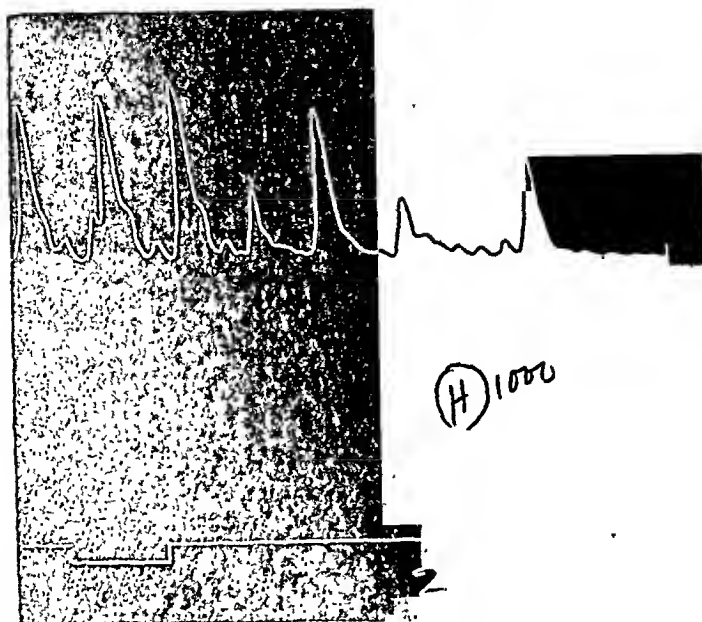


Fig. 4.—*Scrophularia marylandica* (figwort); Experiment 88b, late pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "2"; no contractions were made for ten minutes after the end of the tracing, when the experiment was terminated.

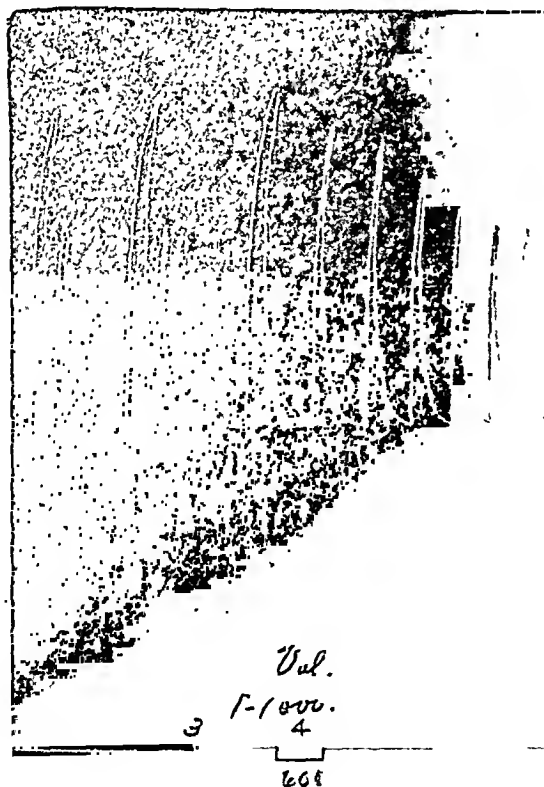
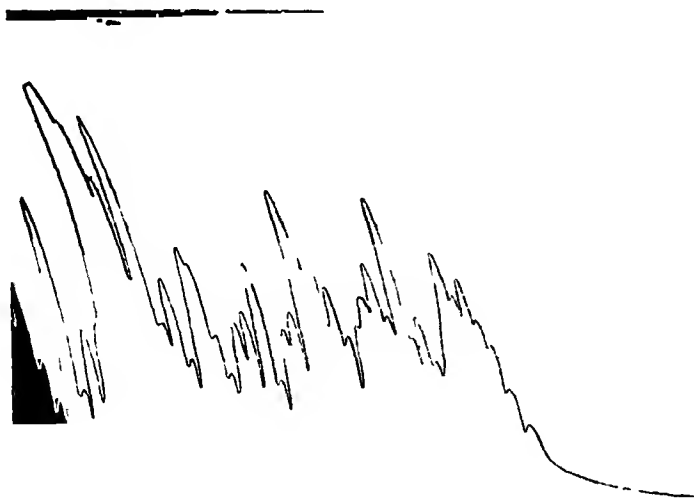


Fig. 5.—*Valeriana officinalis* (valerian); Experiment 51b, about midterm; the fluidextract to make 1 to 1,000 solution was added at "3"; "4" is a time tracing of sixty seconds.

stages of pregnancy. There are, however, instances of very great amplitude of excursion with rapid rate, so that here, too, an increase in tone may be more apparent than real. With this one exception, the impression that we have gained from this work is that the amplitude of the excursion is of greater import in judging the action of a drug than is the effect on the tone of the muscle. Indeed, it seems to us



Oil of Valerian
1-50,000

1 60"

Fig. 6.—Oil of valerian; Experiment 109f, late pregnancy; oil of valerian to make a 1 to 50,000 solution introduced at "1"; the strip made a few small contractions later.

that there may be an actual muscular depression with apparent increase of the tone, for there are instances of an increased rate with a decreased amplitude of excursion in which the strip does not relax to the original state for lack of time only.

A good illustration in point is furnished by the work of Lieb² on viburnum. Lieb states that this drug increases the rate and tone, but diminishes the amplitude; the impression is that the drug really stimulates. Judging from his illustration, we conclude that there is no stimulation, for we think that fre-

2. Lieb: Am. Jour. Obst., 1914, lxi, 28.

quent small contractions are much less efficacious than fewer more vigorous ones, in expelling a fetus at any rate.

Of course, variation in amplitude (decrease or increase) may be balanced by variation in rate (increase or decrease), so that the end-result is practically the same. The points in question are well illustrated in the valerian series. This drug, with very few exceptions, considerably lessened the amplitude of the excursions, while the tone was unaffected in somewhat more than one half the experiments, and occasionally apparently increased. However, the tone



Fig. 7.—*Cypripedium pubescens* (lady's-slipper); Experiment 93d, late pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "1"; no contractions were made for six minutes after the end of the tracing; this is a greater depression than the average experiment shows; "2" is a time tracing of sixty seconds.

was decreased, as a rule, in those experiments in which there was a decreased rate, thus allowing time for more complete relaxation of the muscular strip. On the other hand, the tone was unaffected or occasionally even increased when the rate was somewhat increased (this usually secondary to a considerably lessened amplitude). When the rate was unchanged the tone was lessened. There were exceptions to these generalizations.

Natural Variations in Control Experiments: The action of the muscular strips varies greatly in uniformity. Frequently the rate and amplitude of contraction were quite uniform, but again very irregular. A uterus that had been contracting regularly for several minutes would miss a few contractions, or, vice versa, a strip that had been contracting poorly would begin regular vigorous contractions. This irregularity of action necessitated a large number of experiments to prevent such natural variations being taken for the action of the introduced drug,

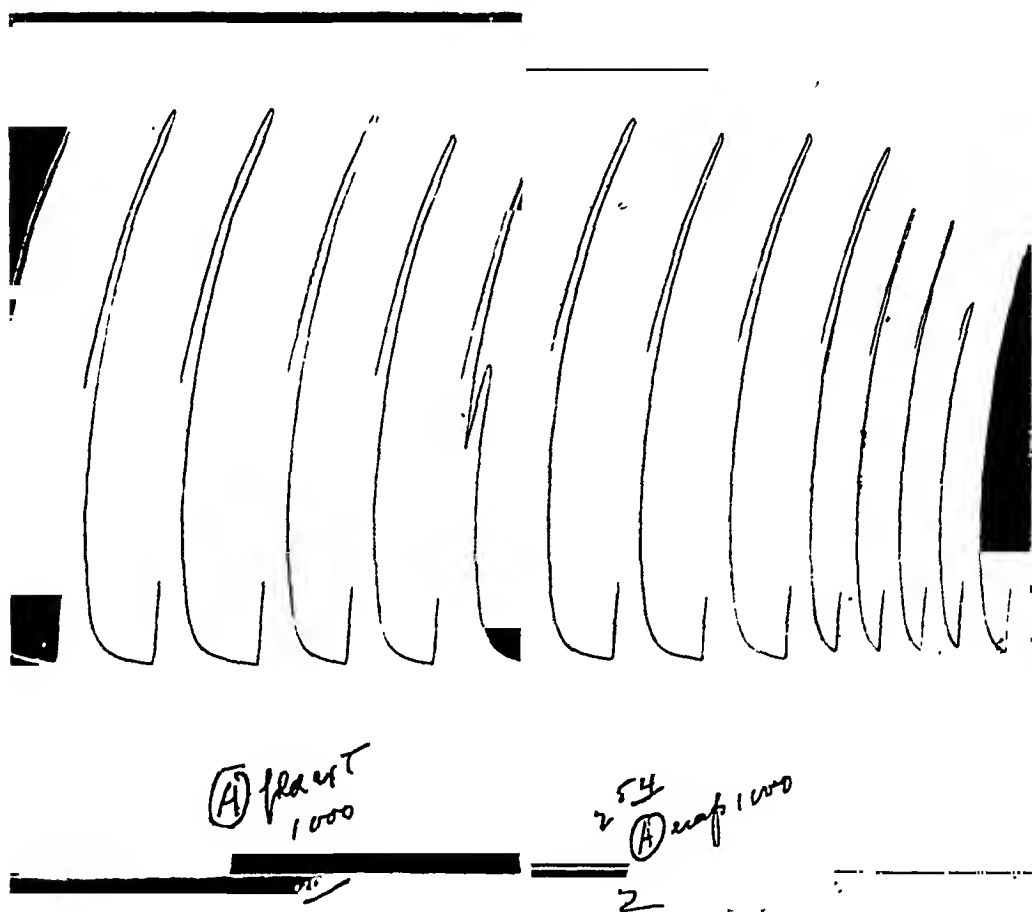


Fig. 8.—*Dioscorea villosa* (wild yam); Experiment 63b, advanced pregnancy; *Dioscorea villosa* (fluidextract) 1 to 1,000 added at "1"; at "2" the evaporated fluidextract to make 1 to 500; the tracing is interrupted for a few minutes between "1" and "2."

for not infrequently on the addition of one of the inert drugs the action changed materially, either a great increase or decrease in function, so without careful control experiments erroneous interpretations might have been made. When such results occurred with the same drug, it is significant that they were not always in the same direction, some tending toward depression and others toward stimulation of one or more functions. Frequently on transferring a strip to fresh stock

solution contractions ceased for a longer or shorter time or their character was changed completely. While the experiments with alcohol indicate that the alcoholic content of the fluidextracts played no definite part in the results, yet it may be that an occasional variable result may have been due to the alcohol. The text will show that this was but an occasional factor, if it played any part at all. Infrequently strips went into tonic contraction of indefinite duration when placed into a fresh bath. In this state they were very resistant to depressant drugs.

In view of the many natural variations, it seems best not to attempt too exact a classification, so that experimental results were considered to be negative unless they were fairly constant in nature. The experi-



Fig. 9.—*Senecio aureus* (life root); Experiment 26a, early pregnancy; *Senecio aureus* (fluidextract) to make a 1 to 1,000 solution added at "2," and, fifteen minutes later, to make a 1 to 500 solution, at "3"; the tracing was interrupted between "2" and "3."

ments are all listed in the accompanying table, as to rate, amplitude and tone, with the different preparations of the drug and the strength of the solution used.

The Results of the Experiments: These are arranged in the text according to the degree of activity of the drug, presenting, first, those drugs that depress, the single drug that stimulates, and finally the inactive preparations:

The Depressant Group: The following drugs are markedly depressant: *Aletris farinosa*, *Pulsatilla pratensis*, *Scrophularia nodosa* and *Ichthyomethia piscipula*; somewhat less active: *Valeriana officinalis* (the oil is very active) and *Cypripedium pubescens*; possessing but slight activity: *Dioscorea villosa*, *Scutellaria lateriflora* and *Senecio aureus*.

The single stimulant drug is *Caulophyllum thalictroides*.

The inactive drugs are as follows: *Chamelirium luteum*, *Leonurus cardiaca*, *Passiflora incarnata*, *Mitchella repens*, *Viburnum prunifolium* and *V. opulus*, *Acer spicatum*, *Cnicus benedictus*, *Carduus marianus* and *Castanea dentata*.

Aletris farinosa (unicorn root): Unicorn root is an active depressant (Fig. 1). The 1 to 1,000 solution of the fluidextract decreased

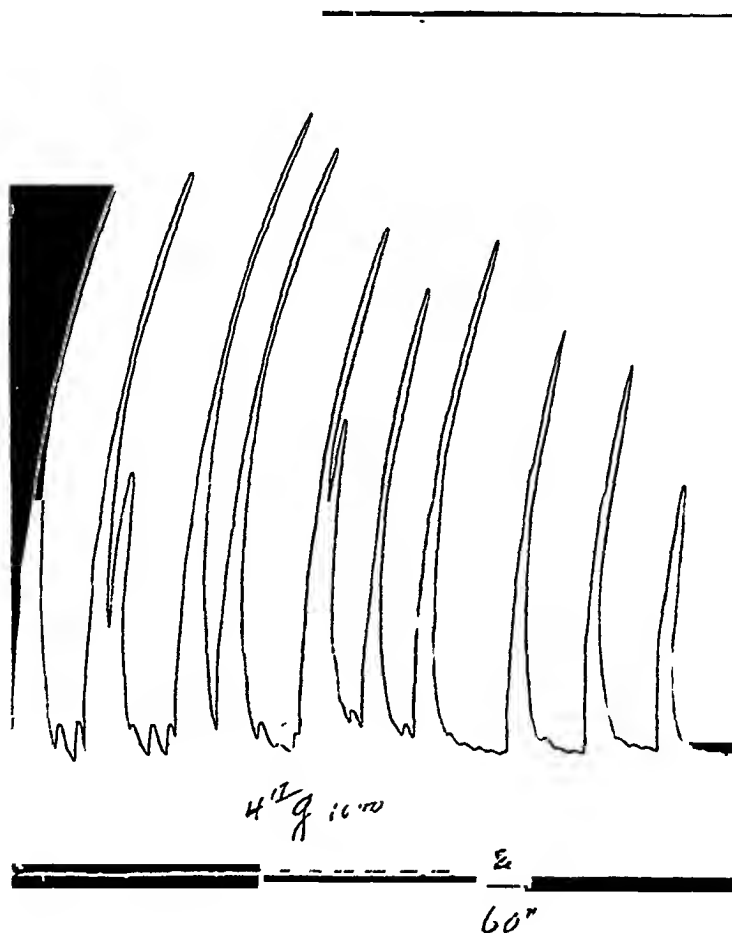


Fig. 10.—*Scutellaria lateriflora* (skullcap); Experiment 88a, late pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds. The action is usually less marked than in this tracing.

the amplitude of excursion in each of thirteen experiments. The results were not quite so uniform with the evaporated extract, but when the solution was increased to 1 to 500 two of the negative experiments also showed depression. The decrease in the amplitude was considerable, being quite marked in about one-half the cases; several times the contractions were interrupted on the addition of the drug and were not resumed at all. The tone was practically not affected.

The rate was usually decreased with the alcoholic preparations, but often unaffected when the evaporated extract was used. The infusion was inactive.

Pulsatilla pratensis (pulsatilla): Pulsatilla is a very active depressant, although the strips from different pigs did not react quite uniformly. The action is the same as that of the other depressant drugs, differing only in degree. Even a 1 to 2,000 solution caused a marked depression in excursion in the two experiments in which it was used (Fig. 2). When effective, the decrease in the amplitude was usually



Fig. 11.—*Caulophyllum thalictroides* (blue cohosh); Experiment 84a; the infusion to make a 1 to 500 solution was added at "2" and the fluidextract to make a 1 to 1,000 solution (of the extract alone) was added at "3." The tracing shows the inactivity of the infusion and the great activity of the alcoholic preparation; the increase in tone was not due to the combined action of the infusion and the fluidextract, for the former was uniformly inactive and the latter always active.

quite prompt and considerable; once the activity ceased promptly on the addition of the 1 to 1,000 solution and was not renewed. The tone was not affected; the rate was slowed in about one-half the cases. The infusion was quite inactive in five experiments, four of them with the 1 to 500 solution and one with the 1 to 1,000.

The action was uniformly depressant on eight strips from two pigs, but with a third pig the contractions of three of six strips were not influenced by the 1 to 1,000 solution, while the others were depressed much less than the strips from the other pigs with the same strength of solution. Two of the

latter strips ceased to contract at once when the solution was increased to 1 to 500, but a third strip, aside from missing two or three contractions on the addition of the drug, contracted practically normally during about twenty minutes. The difference in the reaction in the three pigs is not explainable by the stage of pregnancy.

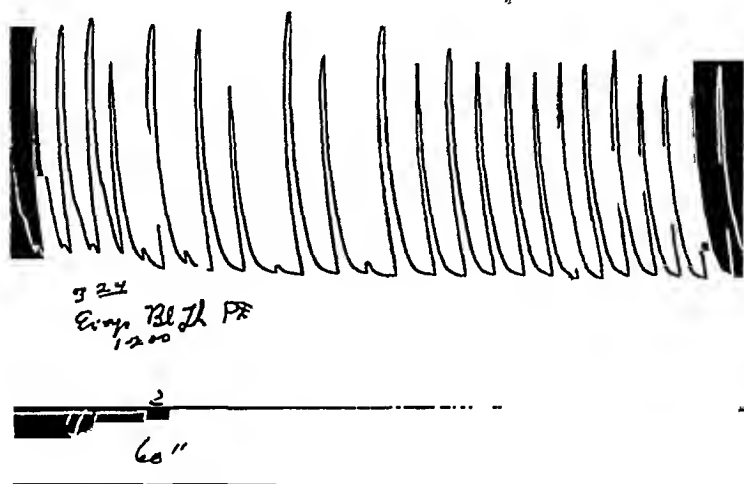


Fig. 12.—*Cnicus benedictus* (blessed thistle); Experiment 95c, about mid-term; the evaporated fluidextract to make a 1 to 200 solution was added at "1"; "2" is a time tracing of sixty seconds.

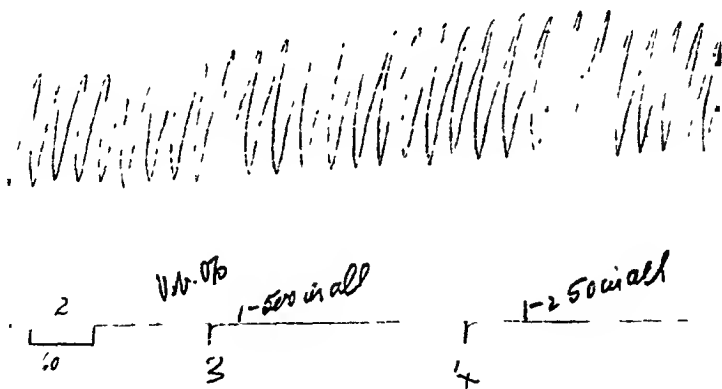


Fig. 13.—*Viburnum opulus* (cramp bark); Experiment 4, virgin cat; *Viburnum opulus* (fluidextract) to make a 1 to 500 solution added at "3," and to make a 1 to 250 solution at "4"; "2" is a time tracing of sixty seconds. (There seemed to be a progressive increase in tone and amplitude when the drug was added.)

Ichthyomethia piscipula (Jamaica dogwood): This preparation is an active depressant; on the addition of the 1 to 1,000 solution of the fluidextract after one or two less vigorous contractions, they cease entirely (Fig. 3). This was the result in five cases, four strips of which were allowed to remain in the solution for forty-five minutes

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON THE TONE OF THE STRIPS OF THE UTERUS *

Drug	Strength of Solution	Number of Experiments	Rate			Amplitude			Tone		
			Increase	Decrease	Negative	Increase	Decrease	Negative	Increase	Decrease	Negative
Iris farinosa— Fluidextract.....	1 to 1,000	13	2	6	3	0	13	0	1	3	9
Fluidextract, evap.	1 to 1,000	12	1	2	9	1	8	3	0	0	12
Fluidextract, evap.	1 to 500	3	2	1	0	0	3	0	0	0	3
Infusion.....	1 to 1,000	2	1	0	1	0	1	1	0	0	2
Infusion.....	1 to 500	2	0	0	2	0	0	2	0	0	2
Matricaria— Fluidextract.....	1 to 2,000	2	1	1	0	0	2	0	0	0	2
Fluidextract.....	1 to 1,000	12	1	6	5	0	9	3	0	3	9
Fluidextract.....	1 to 500	2	0	1	1	0	1	1	0	1	1
Infusion.....	1 to 500	5	0	0	5	0	0	5	0	0	5
Thymethia— Fluidextract.....	1 to 1,000	5	0	5	0	0	5	0	4	0	1
Infusion.....	1 to 500	2	1	1	0	0	1	1	0	0	2
Opuntia— Fluidextract.....	1 to 1,000	8	0	4	4	0	8	0	0	2	6
Infusion.....	1 to 1,000	3	0	0	3	0	3	0	0	0	3
Infusion.....	1 to 500	3	1	1	1	0	3	0	0	0	3
Valerian— Fluidextract.....	1 to 2,000	5	0	2	3	0	2	3	0	2	3
Fluidextract.....	1 to 1,000	29	5	13	11	4	22	3	2	11	16
Fluidextract.....	1 to 500	14	3	9	2	0	14	0	1	12	1
Fluidextract, evap.	1 to 1,000	21	4	11	6	0	20	1	1	12	8
Fluidextract, evap.	1 to 500	6	1	1	4	0	6	0	1	1	4
Infusion.....	1 to 1,000	12	1	1	10	3	0	9	1	0	11
Infusion.....	1 to 500	8	2	1	5	1	1	6	1	0	7
Oil of valerian.....	1 to 100,000	1	0	1	0	0	1	0	0	1	0
Oil of valerian.....	1 to 50,000	4	1	3	0	0	4	0	0	3	1
Oil of valerian.....	1 to 10,000	10	0	10	0	0	10	0	0	10	0
Urtica— Fluidextract.....	1 to 1,000	8	1	5	2	0	8	6	0	0	8
Fluidextract.....	1 to 500	2	0	1	1	0	2	6	0	0	2
Infusion.....	1 to 500	3	1	0	2	0	3	0	0	0	3
Urtica— Fluidextract.....	1 to 1,000	9	0	5	4	1	6	2	0	0	9
Fluidextract.....	1 to 500	2	0	2	0	0	2	0	0	1	1
Fluidextract, evap.	1 to 1,000	4	1	1	2	0	1	3	0	0	4
Infusion.....	1 to 500	6	0	1	5	0	2	4	0	0	6

* The interpretation of the results will be found in the text.

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON THE TONE OF THE STRIPS OF THE UTERUS*—(Continued)

Drug	Strength of Solution	Number of Experiments	Rate			Amplitude			Tone		
			In-crease	De-crease	Nega-tive	In-crease	De-crease	Nega-tive	In-crease	De-crease	Nega-tive
Dioscorea—											
Fluidextract.....	1 to 1,000	14	6	1	7	0	8	6	3	0	11
Fluidextract, evap.	1 to 1,000	5	3	0	2	0	2	3	2	0	3
Fluidextract, evap.	1 to 500	3	1	0	2	0	2	1	0	0	3
Infusion.....	1 to 1,000	3	0	0	3	0	0	3	0	0	3
Infusion.....	1 to 500	2	1	0	1	0	1	1	1	0	1
Senecia aureus—											
Fluidextract.....	1 to 1,000	11	2	2	7	2	4	5	3	4	4
Fluidextract.....	1 to 500	8	1	4	3	1	7	0	1	6	1
Fluidextract, evap.	1 to 1,000	6	0	0	6	0	0	6	0	0	6
Fluidextract, evap.	1 to 500	3	0	1	2	0	2	1	0	0	3
Infusion.....	1 to 1,000	5	0	0	5	1	1	3	1	0	4
Infusion.....	1 to 500	8	2	0	6	1	2	5	2	0	6
Caulophyllum—											
Fluidextract.....	1 to 2,000	3	0	3	0	0	3	0	3	0	0
Fluidextract.....	1 to 1,000	11	0	5	6	0	8	3	11	0	0
Fluidextract, evap.	1 to 1,000	8	0	8	0	0	8	0	8	0	0
Infusion.....	1 to 1,000	4	0	0	4	0	0	4	0	0	4
Infusion.....	1 to 500	4	0	0	4	0	0	4	0	0	4
Viburnum prunifolium—											
Fluidextract (virgin).....	1 to 1,000	5	0	1	4	1	1	3	2	1	2
Fluidextract (pregnant)....	1 to 1,000	8	1	1	6	2	1	5	4	1	3
Fluidextract (virgin).....	1 to 500	5	2	1	2	0	2	3	3	1	1
Fluidextract (pregnant)....	1 to 500	7	1	2	4	1	2	4	2	1	4
Fluidextract, evap.	1 to 1,000	4	0	0	4	1	1	2	0	0	4
Fluidextract, evap.	1 to 500	1	0	0	1	1	0	0	0	1	0
Infusion.....	1 to 1,000	4	0	0	4	2	0	2	0	0	4
Infusion.....	1 to 500	6	0	0	6	2	0	4	1	0	5
Fluidextract (bark of tree)	1 to 500	4	0	0	4	0	0	4	0	0	4
Infusion (bark of tree)....	1 to 500	5	0	0	5	0	2	3	0	0	5
Viburnum opulus—											
Fluidextract (virgin).....	1 to 1,000	5	0	1	4	0	1	4	3	1	1
Fluidextract (pregnant)....	1 to 1,000	8	2	1	5	2	4	2	0	0	8
Fluidextract (virgin).....	1 to 500	7	1	0	6	2	1	4	4	0	3
Fluidextract (pregnant)....	1 to 500	10	3	2	5	0	6	4	0	0	10
Fluidextract, evap.	1 to 1,000	6	0	1	5	0	1	5	0	0	6
Fluidextract, evap.	1 to 500	2	0	0	2	0	0	2	0	0	2
Fluidextract, evap.	1 to 100	1	1	0	0	0	1	0	1	0	0
Infusion.....	1 to 1,000	1	0	0	1	0	0	1	0	0	1
Infusion.....	1 to 500	4	1	2	1	1	2	1	0	1	2
Infusion.....	1 to 100	1	0	0	1	0	0	1	0	0	1

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON
THE TONE OF THE STRIPS OF THE UTERUS*—(Continued)

Drug	Strength of Solution	Number of Experi- ments	Rate			Amplitude			Tone		
			In- crease	De- crease	Nega- tive	In- crease	De- crease	Nega- tive	In- crease	De- crease	Nega- tive
Meer spleetum—											
Fluidextract.....	1 to 1,000	7	2	0	5	2	0	5	1	2	4
Fluidextract, evap.	1 to 1,000	5	1	1	3	2	0	3	1	1	3
Fluidextract, evap.	1 to 500	2	1	0	1	0	0	2	0	0	3
Meliss benedictus—											
Fluidextract.....	1 to 1,000	8	0	1	8	1	1	7	0	1	8
Fluidextract.....	1 to 500	5	0	2	3	0	2	3	0	2	3
Fluidextract, evap.	1 to 1,000	12	4	1	7	8	0	4	8	0	4
Fluidextract, evap.	1 to 500	6	1	1	4	1	1	4	1	1	4
Fluidextract, evap.	1 to 200	10	0	7	3	0	3	7	0	0	10
Infusion.....	1 to 1,000	11	2	1	8	3	2	6	3	0	8
Infusion.....	1 to 500	6	2	0	4	1	1	4	2	0	4
Phamælium—											
Fluidextract.....	1 to 1,000	12	0	3	9	0	4	8	2	2	8
Fluidextract.....	1 to 500	4	0	1	3	2	1	1	2	1	1
Fluidextract, evap.	1 to 1,000	9	1	2	6	1	3	5	1	0	8
Infusion.....	1 to 1,000	5	0	0	5	0	1	4	1	0	4
Infusion.....	1 to 500	7	1	0	6	1	1	5	2	0	5
Peonurus—											
Fluidextract.....	1 to 1,000	8	2	1	5	0	3	5	0	0	8
Fluidextract, evap.	1 to 1,000	7	1	0	6	1	1	5	0	0	7
Infusion.....	1 to 500	7	4	0	3	0	4	3	1	0	6
Passiflora—											
Fluidextract.....	1 to 1,000	10	1	0	9	0	1	9	0	1	9
Fluidextract, evap.	1 to 1,000	5	0	2	3	2	1	2	2	0	3
Infusion.....	1 to 500	2	0	0	3	1	0	2	2	0	3
Platibella—											
Fluidextract.....	1 to 1,000	7	2	0	5	2	3	2	2	0	5
Fluidextract, evap.	1 to 1,000	7	0	0	7	0	0	7	0	0	7
Infusion.....	1 to 500	3	0	0	3	0	1	2	0	0	3
Pastanæa—											
Fluidextract.....	1 to 1,000	9	0	1	8	1	2	6	0	0	9
Infusion.....	1 to 500	4	0	0	4	0	1	3	0	0	4

and made but one small contraction during that time, showing that the action is persistent. The tone was practically unaffected. The infusion is not so active, for while it depressed one strip considerably, a second was not influenced at all.

Scrophulario marylandica (figwort): Figwort actively lessened the amplitude of the excursions, secondarily decreased the rate and left the tone unaffected (Fig. 4). In each of eight experiments there was a marked decrease in excursion within from ten to fifteen minutes of the addition of the drug (1 to 1,000 of the fluidextract). Occasionally the effect was quite prompt, the contractions ceasing temporarily and then recurring some minutes later with considerably lessened amplitude. The rate was but secondarily affected, more often remaining the

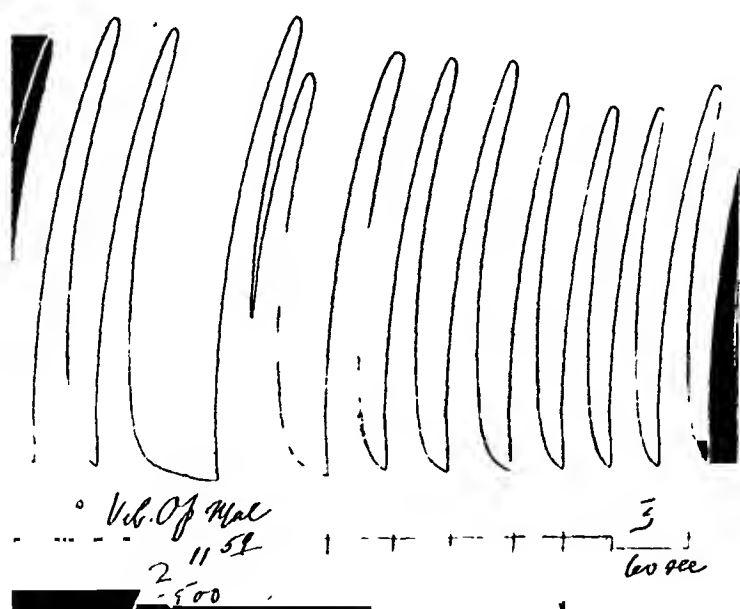


Fig. 14.—*Viburnum opulus* (cramp bark); pregnant guinea-pig; fluidextract *Viburnum opulus* to make a 1 to 500 solution added at "2."

same, but being frequently decreased somewhat. The tone was not altered. The infusion was also effective, as three cases exhibited a somewhat lessened excursion from the 1 to 1,000 solution. This action was augmented by increasing the strength to 1 to 500. When the fluidextract was added to the bath already containing the infusion, the effect was additive.

Valerian: This drug very generally depresses, especially the amplitude of the excursion, somewhat less the tone and the rate. The rate may be increased, presumably secondary to the decreased excursion. The active principle is found in the fluidextract, the evaporated fluidextract, and in the oil of valerian, but not in the infusion; it is non-

volatile at 100 C., for the distillate from the fluidextract is inactive, while the residue retains virtually the original activity. It is probably a resin. Sodium valerate is practically inactive (Figs. 5 and 6).

The Fluidextract: In some fifty experiments with the 1 to 1,000 solution of the fluidextract and the evaporated fluidextract there was uniformly a depression of the muscle strips. The most striking effect was on the amplitude of the excursions, for this was decreased almost without exception, and in practically half the experiments the decrease was rather marked. The non-

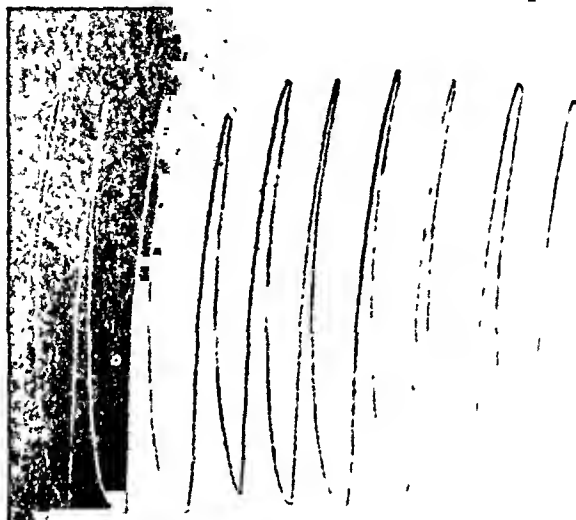


Fig. 15.—*Acer spicatum* (maple bark); Experiment 51b, about midterm; infusion *Acer spicatum* to make a 1 to 250 solution added at "8."

evaporated fluidextract was somewhat more active than the evaporated extract. The rate was also diminished, although in about half the cases only; the action was not so great as on the amplitude. In about one fourth of the cases the rate was moderately increased; however, this did not indicate increase in function, but probably was secondary to the lessened amplitude, as was discussed in the introduction. The muscular tone was also decreased in about one half the experiments, as indicated by the tracings, but, actually, probably much more frequently than this, for the frequently increased rate masked the lessened tone by preventing complete relaxation. Recovery was usually rather

slow and imperfect. With but few exceptions the strips were contracting vigorously. The depressant action was also observed in two of five experiments with the 1 to 2,000 solution of the fluidextract.

As the strength of the solution was increased to 1 to 500 the depressant action became more marked. Of fourteen experiments with the fluidextract, without exception the amplitude was decreased and with but two exceptions the tone also was diminished. The amplitude was lessened in each of six cases with the evaporated extract, although the tone and rate were usually unaffected.

The Infusion: This preparation was inactive in a large series of cases (twelve with the 1 to 1,000 and seven of eight cases with the 1 to 500 solution). The inactivity was not due to the loss of a volatile substance during the

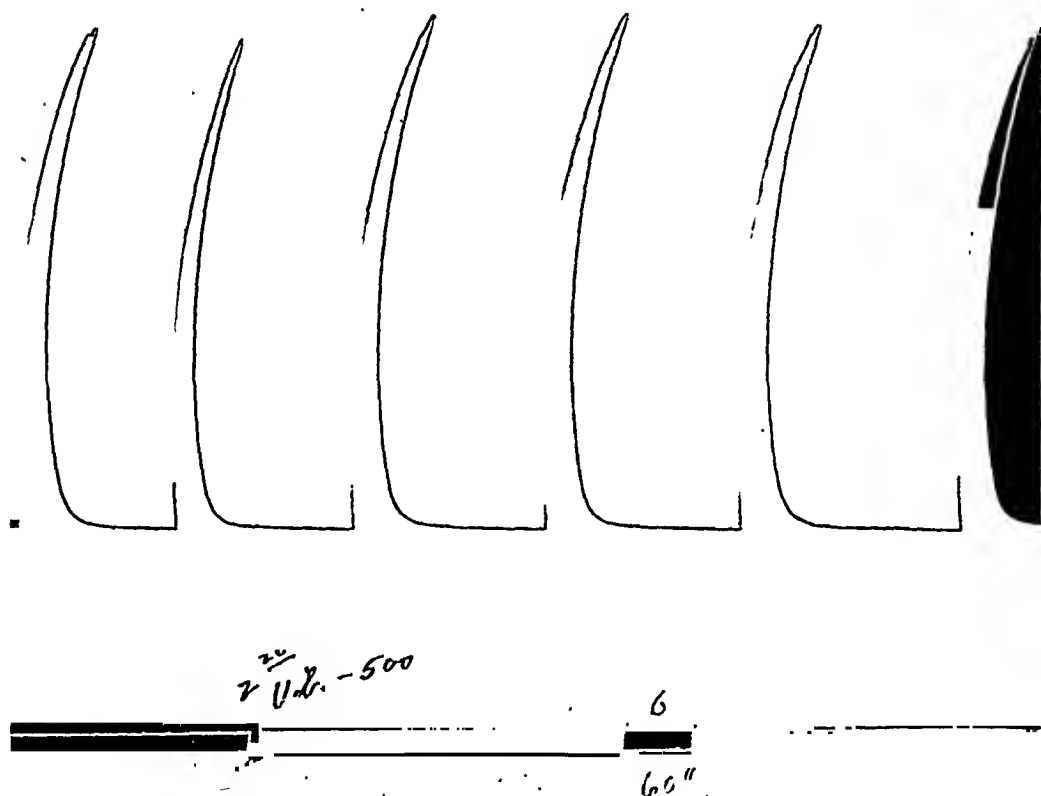


Fig. 16.—*Viburnum prunifolium* (black haw); Experiment 43b, late pregnancy; the fluidextract to make a 1 to 500 solution was added at "5"; fifteen minutes elapsed between the introduction of the drug and the end of the tracing.

making of the infusion, for infusions made in stoppered bottles at 45 C. were inactive. The distillate from the fluidextract was also practically inactive in eleven experiments, while the residue from the distillate, made up to the original volume, preserved practically the original activity of the fluidextract, proving that the active principle of valerian is nonvolatile (at 100 C.), and is not injured by boiling for a short time.

Sodium Valerate: Lieb² states that sodium valerate is inactive except in high concentrations, which are toxic; the actual concentration is not stated. In our work the 1 to 1,000 solution was practically inactive, while the same strength of the fluidextract was always depressant. Three of five experiments with the 1 to 1,000 solution gave negative results and two a slight decrease in

excursion, but one of the latter contracted vigorously after one hour in the valerate. Experiments with less concentrated solutions were negative. Similar strengths were without action on strips that were in a state of high tone.

Oil of Valerian: The oil very actively depresses the strips of the uterus, so that even the 1 to 100,000 solution lowers the amplitude and recovery from the action is very slight when the strips are placed in fresh stock solution. Only one experiment was made with the 1 to 100,000 solution, but as this action was similar to the somewhat stronger solutions, this was thought to be sufficient. The dilution of 1 to 50,000 caused a very marked depression in each of four experiments under different degrees of contractions (Fig. 6). The contractions of two strips were stopped at once, one of which had been contracting moderately and the other but slightly. The vigorous contractions of one strip were inhibited during about twelve minutes. The last strip was in a state of high and increasing tone without contracting and the tone was promptly lowered by the oil. More concentrated solutions allayed contractions at once and recovery was very poor and usually absent if the strip remained in the solution of the oil for even a very few minutes; ten minutes in the 1 to 10,000 solution was usually sufficient to prevent recovery in fresh stock solution. The tone was lowered in all experiments.

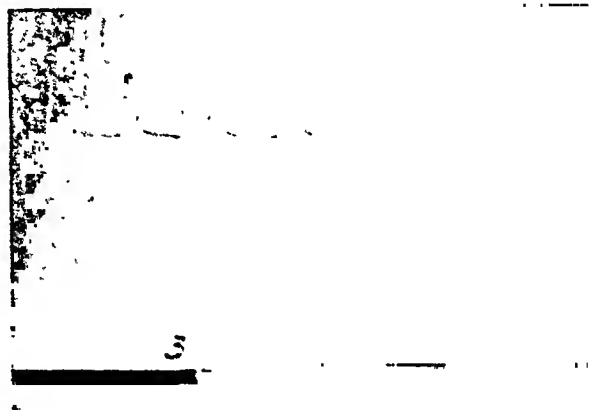


Fig. 17.—*Castanea dentata* (chestnut bark); Experiment 100a, early pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "3."

Cypripedium pubescens (lady's-slipper): Lady's-slipper lessened the amplitude of the excursions moderately but fairly constantly; secondarily, it slowed the rate in part of the experiments and left the tone unaltered. This result was obtained from twelve experiments with the 1 to 1,000 solution of the fluidextract. Two cases showed considerable depression of the amplitude (Fig. 7). The results were the same with vigorously and poorly contracting strips. The infusion in the strength of 1 to 500 also lowered the excursion somewhat.

Dioscorca villosa (wild yam): in about one-half the experiments this drug caused a lowering of the amplitude, in some of them considerably, in others slightly. An increased rate usually accompanied a decreased amplitude, otherwise the rate was not affected (Fig. 8). There was an occasional increase in tone. The results were similar with the fluid and the evaporated extract. The infusion is probably inactive.

The amplitude was lessened in eleven of twenty-two experiments with the 1 to 1,000 solution. In some of them the action was so slight as to be doubtful whether it was not simply a natural variation, rather than an action of the drug. In three of the experiments with lessened amplitude the tone was considerably increased, so that probably the change in excursion was secondary to this; all other experiments were without action on the tone, so that the occasional increase in tone is without significance. Four cases with the 1 to 500 solution gave irregular results. Three experiments with the 1 to 1,000 solution of the infusion were negative; one with the 1 to 500 solution gave an increased tone, but the other was negative. Most of the strips were contracting vigorously, but the initial activity of the strip did not influence the end-result.

Senecio aureus (liferoot): Again the majority of the cases showed this drug to have no constant action on the excised uterus. There was an indication that in high concentrations the drug was depressant.

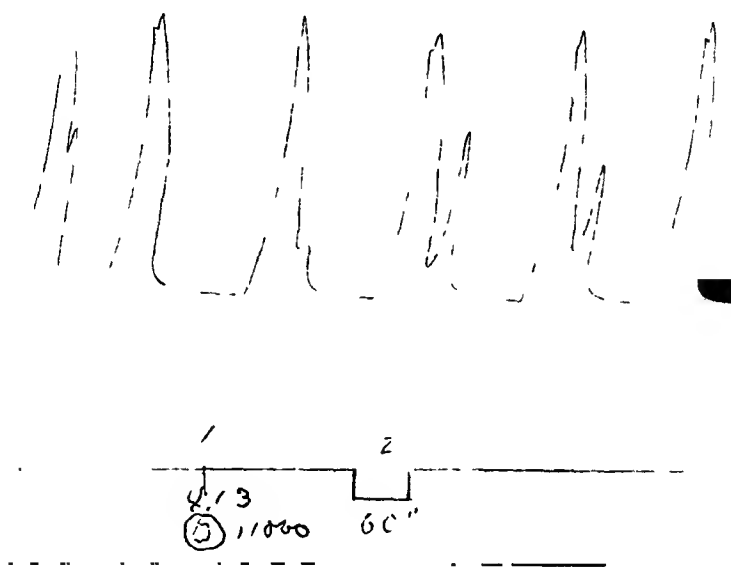


Fig. 18.—*Passiflora incarnata* (passion flower); Experiment 69f, late pregnancy; the fluidextract to make 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds.

With the fluidextract (1 to 1,000) both amplitude and tone were decreased in four of eleven experiments and as the solution was increased to 1 to 500, these functions were decreased in all but one of eight cases (Fig. 9). The depression from the higher concentration was quite marked, although recovery was fairly complete when the strip was placed in fresh stock solution. In the 1 to 1,000 solution neither the infusion nor the evaporated extract exhibited any action on the strips; in the stronger solution (1 to 500) the amplitude was lessened in about one fourth of the experiments with each preparation. Even the 1 to 250 solution was without action on one strip from

the virgin cat uterus during ten minutes and caused but slight decrease in rate and amplitude in a second. A 1 to 1,000 solution of the fluid-extract of the drug made less than a 1 to 2,000 solution of alcohol.

Scutellaria lateriflora (skullcap): This drug exhibited a rather weak and inconstant depressant action (Fig. 10). The excursions were lessened somewhat in about two thirds of the experiments, the rate moderately slowed in one half of them; the tone was not affected. The slight action of the drug is illustrated by the fact that two strips contracted moderately after forty-five minutes in the 1 to 500 solution. Two of six experiments with the infusion 1 to 500 exhibited a slight depression of the amplitude.

Caulophyllum thalictroides (blue cohosh): Blue cohosh invariably caused a pronounced increase of tone or tetanus in all strips that gave any sign of activity and frequently initiated contractions in nonactive strips (Fig. 11). Rather promptly on the addition of the blue cohosh (fluidextract) the contractions either ceased entirely or became greatly lessened in amplitude, as the recording lever rose either considerably

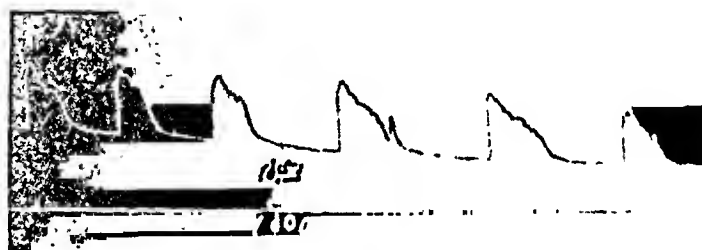


Fig. 19.—*Mitchella repens* (squaw vine); Experiment 70c, about midterm; the fluidextract in a 1 to 1,000 solution.

above, to, or just a little below the maximal point previously attained, but always considerably above the midline between the highest and the lowest levels. Occasionally, when the strip was contracting but slightly or irregularly, the contractions persisted more or less, although the tone was increased. The usual picture, however, was a prompt increase in tone with practically cessation of the contractions, whether the strip had been contracting vigorously or just moderately. The decrease in amplitude, then, seemed to be purely secondary to the marked increase in tone. This tonic state was very persistent, over an hour in a few strips, but the other experiments were usually interrupted after from twenty to forty minutes, so that the strips could be used for other drugs. However, the usual experience was that the strips seldom recovered their normal condition after remaining in the blue cohosh solution for a few minutes. The typical action was caused by the 1 to 2,000 solution in a few experiments.

Further to test the activity of the drug it was added (1 to 1,000) to twelve strips that either had shown no signs of activity after being

in the bath for from twenty to sixty minutes or had ceased to contract after a period of activity; eight of these strips gave the usual increase in tone and four of these also started to contract. The 1 to 1,000 solution also increased the tone of one of three strips that had been rendered inactive by valerian; the cohosh was added directly to the valerian solution.

The infusion was practically inactive in strengths up to 1 to 500. Four experiments were made with the 1 to 1,000 solution, which was increased to 1 to 500. In all cases control experiments, made by adding the alcoholic solution directly to the infusion, gave the characteristic increase in tone. The active principle of the blue cohosh is not extracted in the aqueous preparations.

The experiments were made with uteri in all stages of pregnancy and with the virgin uterus as well. The action was similar in all of the conditions.

Cnicus benedictus (blessed thistle): This drug has practically no action on the excised uterus; even very high concentrations (1 to 200) have little action, but tend toward depression (Fig. 12). The fluid-extract and the infusion were inactive. There was evidence of slight stimulation (increased amplitude and tone) in many of the experiments with the evaporated fluidextract, but this was not sufficiently great to be of significance. All stages of pregnancy were present.

The Fluidextract: The 1 to 1,000 solution was practically inactive, for eight of nine experiments were quite negative and the exception showed but slight depression. The extracts are made with 40 per cent. alcohol, which would make less than a 1 to 2,000 solution in the bath, so that the alcohol could have exerted little if any action. Strengthening the solution to 1 to 500 resulted in moderate depression in two of five experiments. In two experiments on strips from the virgin cat the 1 to 1,000 and the 1 to 500 solutions were without action. Even the 1 to 250 solution was inactive during ten minutes in one case and but slightly lessened the tone in the other. In the latter, however, the contractions were practically unchanged during fifteen minutes, so that the decrease in tone may have been no more than a natural variation.

The Infusion: The results were negative in the majority of cases, both with the 1 to 1,000 and the 1 to 500 solutions. The exceptional results were about equally divided between slight stimulation and depression, that is, probably merely just the natural variations met in control experiments.

The Evaporated Extract: In the 1 to 1,000 solution this increased the amplitude and the tone slightly in two thirds of the experiments (eight of twelve) and increased the rate in one third of them. Part of the increase in function was probably but the normal natural variations, for in some of the experiments there is a probability that the drug was introduced before the curve had become constant. This may explain the difference between the results with the fluid and the evaporated extract. At any rate it is significant that there was no evidence of depression. In view of the uniform inactivity of the fluidextract (in about the same number of experiments) this slight variation can be of no significance. Increasing the strength of the solution to 1 to 500 decreased the number of experiments that showed stimulation to one of six, while four gave negative results and the final one gave depression. With even stronger solutions (1 to 200) there was little permanent action

on the strips, although there was depression of the amplitude in part of them. Two of ten cases were quite negative. In the others one phenomenon was quite constant. On the addition of the drug there was a temporary cessation of the contraction over a period of time corresponding to two or three contractions. Following this brief period one half of the strips returned to the normal condition and remained so during thirty minutes or more, while the others were permanently depressed, considerably in two cases and but slightly in two others. The brief period of cessation of activity could bear little significance in the intact animal unless possibly by an intravenous injection of an enormous dose. The tone was unaffected. The results were similar in vigorously and poorly contracting strips. Citation of a single experiment will illustrate the inactivity of the drug.

Experiment 99: The strip was contracting vigorously. Blessed thistle solution (1 to 200) caused a brief cessation of contraction and then for a short time the contractions were more vigorous than the normal. After ninety minutes the strip was still contracting well although the amplitude was considerably lessened. Two hours later (three and one half hours after the addition of the drug) the strip was still quite active.

Carduus marianus: Several experiments with the 1 to 500 alcoholic solution of the seed of this drug showed it to be without activity.

Viburnum opulus (cramp bark): This drug was probably without action on the excised uterus of the guinea-pig. There was, however, a tendency toward increase in tone in the virgin pig (Fig. 13) and a slight decrease in excursion in the pregnant pig (Fig. 14). In either case the action was neither sufficiently great nor uniform to merit serious consideration, except possibly as it indicated lack of depression on the virgin uterus.

The Virgin Pig: The fluidextract was used. The increase in tone was fairly constant with the 1 to 1,000 solution (four or five cases) and persisted, though with a decreasing percentage, as the solution was increased to 1 to 500. Occasionally the increase was considerable. There was an infrequent and slight increase or decrease in rate and amplitude. In one of two cases with a 1 to 250 solution there was still an increase in tone (rate and amplitude unchanged). In the second the tone was decreased slightly, possibly because there was less time for relaxation as the rate was somewhat increased. Even stronger solutions may show little evidence of depression. A 1 to 100 solution decreased the tone that had been raised by a 1 to 250 solution, but not below the normal. In a second case the tone was considerably increased by a 1 to 100 solution. Too much emphasis should not be placed on the apparent increase in tone from even strong solutions of *Viburnum opulus*, because the limited number of experiments may not exclude the natural variations in action. However, it is significant that there was no depression.

The Pregnant Pig: Two thirds of the cases exhibited a somewhat decreased amplitude with the fluidextract (1 to 1,000 and 1 to 500). The tone was not changed and the rate also was practically uninfluenced. The evaporated extract was without action except in a single case that gave a considerable increase in tone. The infusion was either quite negative or irregular in action, for a few cases showed either slight stimulation or depression. Even a 1 to 100 solution was without action. Practically all the strips from the pregnant uterus were contracting vigorously.

Acer spicatum (maple bark): This drug is said to be substituted for *Viburnum opulus*. It is probably quite void of activity, for in the majority of the experiments with the fluidextract the contractions were

not altered, although in a few experiments the excursions were slightly increased. When the strips were contracting regularly the infusion, even in strong solutions (1 to 250), did not change the curve (Fig. 15).

Viburnum prunifolium (black haw): With the possible exception of an insignificant increase in tone, *Viburnum prunifolium* was without action in this work (Fig. 16). This conclusion was drawn from a total of forty experiments. The slight increase in tone occurred with the fluidextract only, in about one half of twenty experiments. The action was similar in the virgin and the pregnant uteri. The details are found in the table. The increased tone was not secondary to an imperfect relaxation from an increased rate, for the rate was increased in but two of the experiments showing an increased tone. At best, the change in tone was always slight and probably of little significance. There was no evidence of depression in solutions up to 1 to 250 in a single experiment with the virgin cat. The infusion and the evaporated extract were without action in fifteen cases, although one of them gave a slight depression of tone. In the great majority of all experiments the rate and amplitude were unaffected and the variant cases were about equally divided between stimulation and depression.

The bark of the stem was inactive in the 1 to 500 solution of the fluidextract and of the infusion. In two experiments the 1 to 500 solution of both preparations (making a 1 to 250 in all) was inactive. In one experiment the strip was not contracting, but was increasing in tone. The tone remained above normal during fifty minutes' immersion in the viburnum, when oil of valerian (1 to 25,000) promptly lowered the tone below the normal.

Chamaelirium luteum (false unicorn): The results of a large number of experiments with this drug, in 1 to 1,000 and 1 to 500 solutions, demonstrate that it has no constant action. In the far greater number of experiments there was no demonstrable change in the movements of the strip. In the exceptional instances there was no uniformity in the action or in the function affected, indicating that they were in all probability merely natural variations. The variations may be of sufficient merit to discuss, however, for several times there was a marked increase in tone in two virgin and two pregnant uteri, the latter contracting vigorously. The action was especially noticeable in one virgin strip that had been contracting very slightly. Occasionally similar phenomena are met in control experiments, but as it occurred more frequently (four times) with this drug, it may have a little significance. Several times the strips were somewhat depressed, but increasing the solution to 1 to 500 did not further depress, so that such action was probably accidental. These experiments were met a little oftener with the evaporated alcoholic solutions, so that the alcohol was

not the cause of the depression. The infusion (1 to 1,000 and 1 to 500) was inactive.

Leonurus cardiaca (motherwort): The alcoholic solution of the drug were practically inactive, as but three of fifteen experiments gave a moderate decrease in excursion. The infusion (1 to 500) depressed the excursion, as a rule; although this was not marked and in some instances was rather doubtful, nevertheless, there was no sign of a stimulant action. It may be that a principle of slight activity is extracted in the aqueous but not in the alcoholic menstruum.

Castanea dentata (chestnut): The preparation is practically void of action, although occasionally there seemed to be evidence of slight depression. This was not of sufficient intensity to be of any significance (Fig. 17). The infusion was also without action. Nearly all the strips were very active. This preparation was used as an example of an indifferent bark to see whether the tannin or other constituents in any way influenced the activity of the muscular strips.

Passiflora incarnata (passion flower): This is an inactive drug (Fig. 18); nine of ten experiments with the fluidextract were practically negative and the exception gave an immaterial increase in tone and a decrease in amplitude. The evaporated extract gave irregular results and the infusion was negative. All the strips were contracting vigorously.

Mitchella repens (squaw vine): This also is practically inactive (Fig. 19). All experiments with the evaporated extract and the infusion were negative. With the fluidextract the results were somewhat irregular, as in about an equal number of cases there was either no action or an immaterial increase or decrease in excursion. The variations at best were slight and within the limits of the natural variations. The strips usually contracted vigorously, but the less active ones gave the usual results.

CONCLUSIONS

The drugs employed with but one exception manifest their actions on the amplitude of the contractions rather than on the tone or the rate of contraction. The action is essentially the same on the pregnant and on the virgin uterus.

The following drugs lower the amplitude of the excursion, as their primary action: *Aletris farinosa*, *pulsatilla pratensis*, *Scrophularia nodosa* and *Ichthyomethia piscipula* are very active in the strengths used; *Valeriana officinalis* (the oil is very active) and *Cypripedium pubescens* somewhat less active; *Dioscorea villosa*, *Scutellaria lateriflora* and *Senecio aureus* least of all.

Caulophyllum thalictroides puts the strips into tonic contraction or tetanus.

Chamaelirium luteum, *Leonurus cardiaca*, *Passiflora incarnata*, *Mitchella repens*, *Viburnum opulus* and *V. prunifolium*, *Acer spicatum*, *Cnicus benedictus*, *Carduus marianus* and *Castanea dentata* are inactive.

The following infusions only are active and they are less active than the corresponding alcoholic preparations: *Leonurus*, *Scrophularia*, *Ichthyomethia* and *Cypripedium*.

We are glad to express our indebtedness to Prof. Sollmann for reviewing the manuscript.

GLUCOSE FORMATION FROM PROTEIN IN DIABETES *

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1. INTRODUCTION

The origin of carbohydrates from protein in the animal body has become a very firmly established fact in spite of the animated controversies of the past. Proteins have been demonstrated in numerous researches to yield carbohydrates in metabolism. The same holds true for many of the amino-acids, which enter into the constitution of proteins.¹ Indeed there is good existing evidence showing that this is to be regarded as a normal metabolic process.²

It is however in the study of diabetes that a knowledge of sugar formation from protein becomes very essential, for not only is protein food ingested by diabetics converted into glucose, but extensive formation of this monosaccharid is known to take place from the diabetic's own tissue proteins. The importance of these considerations has stimulated numerous experimental investigations. Although much new data have been obtained as a result, considerable obscurity still remains. This applies especially to the question of the exact extent of the conversion of protein into glucose, a weighty subject for a clear conception both of the diabetic process and of diabetic dietetics. In this laboratory during recent years considerable time has therefore been devoted to its study. It is the purpose of the present communication to call attention to the results of medical importance obtained in this work as well as to report further experimental data bearing on the subject of the dietary of diabetes.

2. CRITIQUE OF FORMER INVESTIGATIONS

Previous efforts to ascertain the amount of glucose arising from the breakdown of proteins in metabolism have met with so many experimental difficulties that in almost all cases the results obtained are

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* Preliminary reports of the experiments detailed in this section were presented in papers read before the Society for Experimental Biology and Medicine, Jan. 19, 1916, and the College of Physicians, Philadelphia, June 7, 1916.

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open to serious criticism. It seems therefore expedient rather to emphasize the various sources of error in this work than to indulge in an elaborate critical review, which has indeed been already done by others³ who also quote the literature extensively. The human diabetic has been in the past the subject most frequently selected for experiments of this nature.⁴ Various proteins were fed to glycosuric patients and the influence on the sugar excretion observed. The results showed a rise in the glycosuria following the ingestion of protein, but very little certainty as to the extent of either absolute or relative sugar production from protein can be attached to this work for reasons to be stated.

In order to ascertain by means of feeding experiments the extent of glucose formation from ingested proteins it is necessary to demonstrate that all the fed material is digested and absorbed and that all the glucose arising from this material and no more, originates from this protein. These conditions can hardly be afforded by the human subject, as will now be brought out. In most cases of diabetes mellitus a certain amount of oxidation of glucose takes place. Moreover the capacity of the human diabetic to utilize glucose frequently may undergo considerable daily variation, even when the diet remains the same. It is also possible that glucose originating from food protein may be in part synthetically used in the formation of various body substances or be deposited as glycogen. In regard to these last considerations there are very few definite data as yet on record for the human diabetic.

The reliability of such metabolic experiments is dependent on the complete assimilation of the protein fed. In the former experiments referred to this important matter has not been adequately controlled. The important physiologic factors in this regard will be discussed later in this communication. It may suffice to mention here that the completeness and rapidity of absorption of protein is dependent not only on the amount and physical condition of such food, but also on the nature of other constituents of the diet. Experiments on human diabetic individuals, in which a given amount of protein is superimposed on other diet, are therefore rather uncertain.

It would thus seem advisable to use fasting diabetics for such experiments. The effect of starvation on the human subject is, however, as is so well demonstrated by Allen's researches, immediately to

3. For literature concerning the formation of sugar from protein see the following: Cremer, M.: *Ergebn. d. Physiol.*, 1903, i, 803. Pflüger, A.: *Arch. d. ges. Physiol.*, 1903, xcix, 1; *Ibid.*, 1904, ciii, 1. Langstein, L.: *Ergebn. d. Physiol.*, 1902, i, 63; *Ibid.*, 1904, iii, 453. Falta, W.: *Ztschr. f. d. inn. Med. u. Kinderh.*, 1908, ii, 99.

4. See the work of Luthje, von Noorden, Mohr, Therman, and Falta.

increase the ability of the organism to oxidize glucose. We cannot then expect glucose arising from ingested substances to be excreted quantitatively by otherwise fasting diabetics. This is undoubtedly a source of error in certain human experiments already reported, in which protein has been administered to patients after days of greatly restricted diet. Another and contrary effect of feeding quantities of sugar-forming proteins to diabetics is to lower the tolerance of the organism for glucose, with consequent uncertainty in the results. This is very evident in certain of Mohr's experiments. Still another disturbing factor in the use of the human diabetic is the fact that muscular exercise may decrease the glycosuria under some circumstances, but increase it under others.⁵ But the great difficulty of preventing diabetics breaking diet is very probably the chief cause of error in such human experiments.

Through one or more of these sources of error the results of protein feeding experiments and clinical observations are rendered dubious. Conclusions drawn from these results cannot therefore be regarded as established. Among such may be mentioned those of Lühje, von Noorden, and Falta, who hold that relative differences in the influence of protein food on the glycosuria are observable in light or moderate cases of diabetes. Falta's observations that those protein foods which are more difficult of digestion more favorably influence the glycosuria also illustrates the difficulty of such experimentation. If the alimentary factors had been carefully controlled in these experiments it is probable that very different results would have been obtained.

In endeavoring to avoid these difficulties the depancreatized diabetic dog also has been made use of by other workers. Unfortunately such animals are ill adapted to fine metabolic examinations of this type, for the reason that extirpation of the pancreas is followed by very severe effects, which are indeed particularly marked in case of the digestive system. It is not surprising that no certain results have been obtained by this method of experimentation. There is also considerable evidence which cannot here be detailed, to the effect that a certain amount of glucose utilization does take place locally in depancreatized dogs in spite of data to the contrary.

Glucose formation from ingested protein has also been studied experimentally in a few isolated instances with the aid of dogs made diabetic with the use of the glucosid phlorizin. The work of Halsey,⁶

5. Von Noorden, C.: *Die Zuckerkrankheit und ihre Behandlung*, Berlin, 1912, Ed. 6, p. 100.

6. Halsey, J. T.: *Sitzungsber d. Gesellsch. z. Beförderung d. Gesamten Wissenschaften*, Marburg, 1899, p. 102.

Rohmer⁷ and Bendix⁸ may be referred to. The technic employed is open to various criticisms, which preclude drawing definite conclusions from this work. Reilly, Nolan and Lusk,⁹ however, in two experiments were able to determine the amount of glucose formed from gelatin in metabolism.

3. DEVELOPMENT OF IMPROVED EXPERIMENTAL METHODS

As both the human diabetic and the depancreatized dog represent serious obstacles to the successful study of glucose formation from protein, recourse was made to phlorizin diabetes. Although many experimental difficulties were encountered here also, none proved insurmountable and a technic could be developed by which the extent of protein conversion into glucose could be followed with considerable accuracy. The various details bearing on this point have been dealt with in a preceding series of articles,¹⁰ so a repetition scarcely seems indicated. A few main points, however, may be alluded to, as the nature of phlorizin glycosuria is not so well known to many as are other forms of melituria. This kind of diabetes has been very carefully studied by Lusk and a number of other workers within recent years with the result that its metabolism is now fairly adequately understood. When phlorizin is administered to dogs in the proper manner, complete diabetes rapidly develops, the reserve of carbohydrates within the body is quickly exhausted and in the fasting state the glucose appearing in the urine bears a constant relation to the urinary nitrogen, this so-called glucose-nitrogen ratio averaging 3.4 to 1.¹¹ Glucose administered to such animals within certain limits is quantitatively excreted.¹² Glucose arising from nontoxic ingested substances fails to be stored up or elsewhere utilized, but appears in the urine also quantitatively. This subject has been discussed previously by the writer, who has detailed the reasons for accepting this view.¹³ Recently experiments from this laboratory have been reported, which also make it very probable that all the glucose arising from protein fed to phlorizinized dogs is excreted in their urine.¹⁴ This

7. Rohmer, P.: *Ztschr. f. Biol.*, 1910, liv, 455.

8. Bendix, E.: *Arch. f. Physiol.*, Supplement, 1900, 309.

9. Reilly, F. H., Nolan, F. W., and Lusk, G.: *Am. Jour. Physiol.*, 1898, i, 405.

10. Janney, N. W.: *Jour. Biol. Chem.*, 1915, xx, 321. Janney, N. W., and Csonka, F. A.: *Ibid.*, xxii, 203. Janney, N. W., and Blatherwick, N. R.: *Ibid.*, xxiii, 77.

11. The glucose-nitrogen ratio of 3.65 to 1 has been established by Lusk for the fasting phlorizinized dog and has been generally accepted. From the larger number of observations now on record, however, the slightly lower value of 3.4 to 1 has been found by Janney and Csonka to be more nearly correct.

12. Ringer, A. I.: *Jour. Biol. Chem.*, 1912, xxii, 422.

13. Footnote 10, first reference.

14. Footnote 10, second reference.

work demonstrated that the urinary glucose and nitrogen of fasting phlorizinized animals, which quantitatively excrete ingested sugar, bear the same relation to each other as the extra glucose arising from these animals' own proteins ingested by other phlorizinized dogs does to the nitrogen contained in these proteins. In other words, just as much glucose appears in the urine after ingestion of phlorizinized dogs' proteins as is yielded by the breakdown of the fasting animals' living protoplasm. Such identical results would be impossible if all the glucose originating from the ingested proteins did not appear in the urine, for we have reason to believe that carbohydrates are not stored by fasting phlorizinized dogs (Lusk). Consequently the sugar excreted represents the maximal amount formed from the animal's body proteins.

Recently it has been shown by Sansum and Woodyatt¹⁵ that the rise in glycosuria following ingestion of various toxic substances is not necessarily to be ascribed to sugar formation from these substances. The results obtained in the experiments to be discussed in this article are, however, not subject to this criticism, as only innocuous food substances usually representing normal constituents of animal diet were fed in this case.

In order to determine quantitatively the amount of glucose arising in diabetic metabolism from a given protein on ingestion, it is also necessary to demonstrate that at least under the experimental conditions employed complete digestion of the material fed has taken place, together with absorption and elimination of the digestive products arising from it. In this regard a variety of physiologic factors are now known to play a part. The researches of Mendel and co-workers have demonstrated that the rate and thoroughness of protein digestion is mainly dependent on the volume and texture of the material fed, as well as on the presence in the alimentary tract of other food and indigestible substances. It has also been shown that even the amount of water taken can markedly influence digestion.¹⁶ When these factors are considered, however, digestion and absorption of proteins, whether of animal or vegetable origin, are with but few exceptions very similar.¹⁷ These data were mostly unknown at the time when the chief part of the previous experimentation on glucose formation took place and represent an uncontrolled source of error in many of these experiments. In our preliminary studies due consideration, however, was given these physical factors. The experiments have therefore been made throughout this entire series of investigations on fasting animals and due care given to the quantity, volume and texture of the proteins fed. The

15. Sansum, W. D., and Woodyatt, R. T.: *Jour. Biol. Chem.*, 1915, xxi, 1.

16. Bergeim, O., Reh fuss, M. E., and Hawk, P. B.: *Jour. Biol. Chem.*, 1914, xix, 345.

17. Mendel, L. B., and Lewis, R. C.: *Jour. Biol. Chem.*, 1913-1914, xiv, 55.

water intake was also properly regulated. In a series of preliminary control experiments the hourly nitrogen and glucose elimination were also followed and exact time limits established which insured the excretion of these products arising from the ingested proteins. It was found possible in this way so to refine the technic that the glucose arising from proteins in the metabolism of the living animal could be determined with as great degree of accuracy as accompanies certain analytic procedures.

Inasmuch as the value of many recent diabetic researches, including the present studies, depends on how directly the experimental results obtained for phlorizin diabetes are applicable to human diabetes, a few remarks relative to this subject are not out of place. As is well known, various differences exist between these two forms of glycosuria. A detailed comparison of these conditions cannot, however, be entered into in the present article. The data bearing on this subject has been collected and ably discussed by Allen,¹⁸ to whose monograph reference may be made. The writer's standpoint concerning the nature of phlorizin glycosuria may, however, be briefly stated as follows.

Phlorizin diabetes is produced by the action of the glucosid of this name and is regarded by many to be of renal origin, in sharp distinction to diabetes mellitus. This view, however, requires modification. According to Biedl and Kolisch¹⁹ the liver forms glucose when perfused with fluid containing phlorizin. The writer²⁰ has observed that the glucose content of blood to which phlorizin has been added increases on perfusion through muscle. Underhill²¹ has found considerable glucose formation to take place in phlorizinized animals in which the kidney function was eliminated. It has been fully demonstrated by Lusk in various ways that the body proteins are the source of sugar excreted by fasting phlorizinized dogs. From these and further facts which could be adduced the conclusion can be drawn that phlorizin affects the tissues of the body as a whole with sugar synthesis as a result. Phlorizin diabetes is therefore to be regarded just as is diabetes mellitus, a morbid process of general nature, characterized by glucose formation from protein.

The effect of phlorizin on the kidney has been the object of many investigations. The various data and arguments on this subject also cannot here be discussed. It may be but briefly emphasized that the importance of the kidney in phlorizin diabetes, though very great, has been overestimated, for neither sugar formation in this organ nor indeed in the blood can adequately account for the production of such

18. Allen, F. M.: *Glycosuria and Diabetes*, Boston, 1913.

19. Biedl, A., and Kolisch, R.: *Verhandl. d. 18 Cong. f. inn. Med.*, 1900, 573.

20. The author's unpublished experiments.

21. Underhill, F. P.: *Jour. Biol. Chem.*, 1912, xiii, 15.

large amounts of glucose as are excreted in this form of diabetes. The local action of phlorizin on the renal organs is, however, in all probability responsible for several of the chief differences observed between this and the human form of diabetes. The hypoglycemia and various phenomena connected with glycosuria and diuresis characteristic of phlorizin diabetes are thus best explainable as the result of the toxic effect of this glucosid on the renal function.

In further comparing these two forms of diabetes the lack of the clinical symptoms of diabetes mellitus in phlorizin glycosuria cannot be fairly regarded as representing a fundamental difference for the following reason: In judging of this side of the question it must be remembered that it is difficult properly to compare the reaction of a dog subjected for a short period of time to phlorizin injections with the eminently chronic manifestations of human diabetes. Many signs of human diabetes, however, are actually to be observed in phlorizinized dogs. Such are rapid loss of weight, polyuria, and at times polyphagia, thirst, delay in the healing of wounds, and tendency to local infections. Even cataract has been noted.²² A further discussion of this important subject cannot be entered into here. There are good grounds, however, for accepting that phlorizin diabetes has many of the characteristics which would reasonably be ascribed to diabetes mellitus of the same intensity and duration, if such an acute form of human glycosuria were known. However, no attempt to establish the identity of these conditions can be reasonably made. On the other hand, sufficient evidence, it is believed, has been advanced to show that these morbid processes are much more closely related than is generally recognized.

Aside, however, from the general nature of these two expressions of diabetes, and especially in regard to glucose formation from protein, previous studies make it very probable that this process is essentially the same in both severe human and phlorizin diabetes. Body proteins break down in either case with the liberation of nitrogen and glucose in like amounts in both these conditions.²³ Glucose formation from ingested proteins has likewise been demonstrated to take place in phlorizin as well as human diabetes. The relation of the urinary glucose to the nitrogen, or glucose-nitrogen ratio, has been repeatedly recorded as practically the same for either condition when of maximum development.²⁴ A human case of phlorizin diabetes showed the same glucose-nitrogen ratio.²⁵ It is very probable that more similarities of

22. Lusk, G.: Verbal communication to the author.

23. Footnote 10, last reference.

24. For literature see Allen, F. M., and Du Bois, E. F.: *Metabolism and Treatment in Diabetes*, *THE ARCHIVES INT. MED.*, 1916, xvii, 1010.

25. Benedict, S. R., and Lewis, R. C.: *Proc. Soc. Exper. Biol. and Med.*, 1913-1914, xi, 134.

like nature would have been brought out did human beings not present so many difficulties with regard to exact experimental study.

Granting then that the body proteins of diabetic man and the phlorizinized dog yield about the same amount of glucose in metabolism, does the same hold true for ingested proteins? We believe this is to be answered in the affirmative for the following reasons: It has been demonstrated in this laboratory²⁶ that very nearly the same amount of glucose was formed in phlorizinized dogs from the proteins of the living animal and from muscle protein, that is, from the chief bulk of body protein of either dog or man when fed to phlorizinized dogs. This work makes it very probable the glucose formation from proteins ingested by man is not likely to be different from that occurring in the dog, providing no fundamental differences exist in protein metabolism in general between these two species. This point is covered by the work of Osterberg and Wolf,²⁷ among others, who in elaborate studies could discover no salient differences between the canine and human in this respect. For these and other grounds we deem it justifiable to apply to the problems of diabetes mellitus the results of careful protein feeding experiments made on dogs having phlorizin diabetes.

4. GLUCOSE FORMATION FROM ISOLATED PROTEINS

After thus satisfying ourselves as to the reliability of the technic employed as well as to the value of the data obtained by this mode of experimentation, a representative group of chemically pure, isolated proteins was fed in a series of more than seventy metabolic experiments to diabetic dogs and the glucose yielded in the metabolism of the proteins ascertained. The proteins employed and the results obtained are shown in Table 1, which is taken from a preceding article.

TABLE 1.—GLUCOSE YIELDS OF INGESTED PROTEINS

	Casein	Ovalbumin	Serum Albumin	Gelatin	Fibrin	Edestin (Hemp Protein)	Glutadin (Wheat Protein)	Zein (Corn Protein)
Glucose yield in per cent.	48	54	55	65	53	65	80	53

This investigation clearly established the important fact that no difference in their sugar-producing capacity exists between animal and vegetable proteins owing to their respective origins. The amount of glucose yielded in metabolism could, however, be demonstrated to vary directly with the amount of glucogenetic amino-acids contained in each

26. Footnote 10, second and third references.

27. Wolf, C. G. T., and Osterberg, E.: *Biochem. Ztschr.*, 1911, xxxv, 329.

individual protein. Thus the wheat protein gliadin contains 43.7 per cent. glutamic acid, which is known to yield large amounts of glucose in metabolism. Gliadin yields the largest amount of glucose of all proteins hitherto examined. This is chiefly due to the large amount of this amino-acid present. Application of these new facts to the diabetic's dietary will be made in the latter part of this article.

Source of the Glucose Arising from Protein.—At various times in the medical literature discussions have arisen as to what part of the protein molecule yielded sugar, and particularly as to whether the carbohydrate content of protein could be responsible for the metabolic glucose originating from this food class. This question can, in view of the experiments just recorded, be regarded as definitely settled in the negative. Through the studies of Lusk, Dakin and others¹ it has been conclusively demonstrated that the majority of the amino-acids entering into the constitution of proteins yield glucose in metabolism. Our own work has demonstrated the fact just alluded to, that the amount of sugar so formed from proteins is dependent on the amount of glucose-yielding amino-acids entering into the make-up of each particular protein.¹³ Indeed, according to recent studies in the chemistry of proteins, carbohydrate as such is present in very insignificant amounts and is to be rather regarded as an impurity than a component part of the protein molecule. This fact has been borne out by our metabolic experiments in which pure ovalbumin was fed. This protein was formerly thought to contain considerable carbohydrate, but our results show that it yields actually less glucose than various other albuminous substances to which a carbohydrate group has never been ascribed. This is a point which seems as yet little known among authorities on diabetes. Thus von Noorden,²⁸ as late as 1912, believed that a carbohydrate group plays a rôle in glucose formation from protein.

5. GLUCOSE FORMATION FROM BODY PROTEINS; THE GLUCOSE-NITROGEN RATIO

The origin of the glucose excreted in diabetes has held the attention of investigators for generations. Proteins and fat are to be regarded as the chief possible sources of endogenous glucose excretion. In order to ascertain what amount of the glycosuria could be ascribed to protein and what to fat, the urinary nitrogen elimination has been studied in relation to that of sugar, that is, the glucose-nitrogen ratio. This has been done in order to determine the maximal amount of the sugar production from protein. Sugar excreted in excess of this maximum could be ascribed to fat.

28. Von Noorden, C.: *New Aspects of Diabetes*, New York, 1912. Umber, F.: *Therapie d. Gegenwart*, 1901, iii, 440.

But efforts to determine how much glucose can arise from protein through study of the urinary glucose-nitrogen ratio have met with many difficulties. Minkowski found that fasting depancreatized dogs excreted glucose in relation to nitrogen as 2.8 to 1, and therefore calculated 45 per cent. as the maximal amount of body protein convertible into glucose. Lusk, using phlorizinized dogs, established the glucose-nitrogen ratio as 3.65 to 1, corresponding to a conversion of 58.5 per cent. of protein into sugar. Similar studies carried out on human diabetics have led to the vaguest results. Thus glucose-nitrogen ratios have been reported varying all the way from 0.01 to 1 to 12 to 1. Owing to this uncertainty, most authors on diabetes attach at present very little weight to the importance of the glucose-nitrogen ratio.²⁸ With the aid of the improved technic already alluded to, the problem of the maximal formation of glucose from protein, however, could be definitely decided. With the same precautions as previously employed in the case of isolated proteins, muscle from various species of animals was fed to phlorizin diabetic dogs and the amount of glucose arising in metabolism ascertained as hitherto. By the aid of a new analytic method²⁹ developed for this purpose, it became possible accurately to determine the amount of protein present in the animal muscle used in these experiments and also to ascertain the nitrogen content of this protein. By this means we were enabled not only definitely to learn how much glucose arises from muscle proteins in metabolism, but what relation this glucose actually bears to the nitrogen of the protein, that is, the real protein glucose-nitrogen ratio, which is not identical with the urinary glucose-nitrogen ratio. The protein glucose-nitrogen ratios for body proteins other than muscle were obtained in a similar manner and were found to average just about the same as in the case of the muscle proteins themselves. In this way the maximal formation of glucose from body proteins could be established by direct experiment. No great variations were found among various species as Table 5, taken from our previous studies, demonstrates. The body proteins of man were thus found to yield 58 per cent. of glucose in the diabetic metabolism, corresponding to the glucose-nitrogen ratio of 3.6 to 1.

It follows from this fact that complete diabetes in man exists when the glucose-nitrogen ratio of the urine is about 3.4 to 1 (Janney and Blatherwick). This glucose-nitrogen quotient now established as a definite value consequently becomes of importance in the study of this disease, as it represents a definite index of its severity. The nearer this ratio as exhibited by fasting diabetics approaches the value 0 to 1 the better the prognosis which may be made. Conversely the persis-

29. Janney, N. W.: *Jour. Biol. Chem.*, 1916, xxv, 177.

tence of a high glucose-nitrogen ratio adds to the gravity with which the case is to be regarded, for not only is a maximal formation of glucose from the body proteins here taking place, but also oxidation of carbohydrates is impossible.

As a result of these studies it is also evident that the urinary ratios higher than about 3.4 to 1 previously reported for human diabetics must be based on erroneous observation. These new investigations are also applicable to the question of sugar formation from fat in diabetes as previously alluded to. Owing to the demonstration that all the glucose and no more which can originate from protein appears in the urine of severe diabetic patients and of fully phlorizinized dogs during a fast, it is evident that fat is not to be regarded as an important source of urinary glucose in diabetes. This coincides with Mandel and Lusk's³⁰ observations that the feeding of large quantities of fat has no influence on the sugar output of phlorizinized dogs. Though from certain fatty acids synthesis of glucose undoubtedly does occur, as has been demonstrated by Ringer and others, glucose formation from fat evidently plays no large part in the diabetic's economy. In the actual treatment of this disease it is known, however, that the addition of fats to the diet can lead to increased glycosuria and ketonuria.³¹ This is, however, very probably to be regarded chiefly as a result of the stimulating action of fat on protein metabolism, for Lusk's³² elaborate respiratory studies have demonstrated that certain intermediary products, which can also arise from fatty acids, act as a stimulus to metabolism. These facts are emphasized inasmuch as considerable doubt exists in regard to the question of sugar formation from fat.

6. GLUCOSE FORMATION FROM PROTEIN FOODS

(With the assistance of F. A. Csonka.)

Glucose Formation from Meats, etc.—The investigations just described have rendered the solution of another very practical problem possible, that is, the exact determination of the amount of glucose produced from meats and other protein foods as a result of their metabolism in the diabetic organism. The detailed results of this study are reported in this communication. Various meats were fed to dogs made completely diabetic by the use of phlorizin and the amounts of glucose arising from the food ascertained under the employment of the same technic and methods as previously employed. These experiments are accordingly not described in full. The meat was prepared for analysis and feeding by removal of all indigestible portions, ground fine in a meat grinder, the amounts for each feeding weighed, and then stewed for one hour on a steam bath. This

30. Mandel, A. R., and Lusk, G.: Jour. Am. Med. Assn., 1904, xliii, 241.

31. Allen, F. M.: Jour. Am. Med. Sc., 1915, iv, 480.

32. Lusk, G.: Jour. Biol. Chem., 1914, 1915, xx, 555.

was done with the idea of obtaining results applicable to cooked food. The eggs for analysis and feeding were hard boiled, and after removal of the shells, were passed through a meat grinder, thoroughly mixed and moistened with water before feeding. In the meat for feeding, nitrogen, total solids and, for the sake of control, the total amount of substances reducing Fehling's solution, as well as the glycogen content, were determined with employment of the same analytic methods as previously. The results of these analyses appear in Table 2.

TABLE 2.—ANALYSIS OF MEAT USED IN FEEDING EXPERIMENTS,
GRAMS PER 100 GM. MEAT *

	Total Solids	Nitrogen	Substances Reducing Fehling's Solution	Glycogen
Lean beef (first two experiments)...	25.35	3.32	0.18	Less than 0.1
Lean beef (last two experiments)...	25.08	3.28	0.18	0.08
Chicken meat.....	25.54	3.7	0.29	Less than 0.1
Fish (halibut).....	22.0	2.98	0.23	Less than 0.1
Chicken egg.....	26.9	2.1	0.31	Less than 0.1

* Analyses of rabbit meat have been published previously, Jour. Biol. Chem., 1915, xxii, 212.

The reducing substances and glycogen were present in too minute amounts to exert any obvious influence on the glucose yielded by the meat fed. This fact we have indeed demonstrated in another way. In earlier experiments muscle proteins were separated in considerable quantity from the other meat constituents and found in similar feeding experiments to give rise to precisely the same amount of glucose as did corresponding amounts of the same sample of meat previous to its being subjected to this procedure. Meat extract has also been demonstrated by Csonka³³ to be not glycogenetic, an important fact to be considered in diabetic dietetics. There is, therefore, no question but that the protein itself represents practically the entire source of the glucose derived from the meat. The meat was fed in very moderate quantities, chosen so as to administer the albuminous substances to the animals in similar amounts as our preliminary studies had demonstrated to be entirely assimilated and the products eliminated within nine hours. Meat is known to be very quickly digested, absorbed and its metabolites excreted by man and animals. Important recent studies of Mendel and Fine³⁴ have demonstrated that when fed in larger quantities than used in these experiments it is utilized to the extent of 100 per cent. by dogs. Lusk and his co-workers⁹ have fed various amounts of meat to fasting

33. Csonka, F. A.: Jour. Biol. Chem., 1915, xx, 539.

34. Mendel, L. B., and Fine, M. S.: Jour. Biol. Chem., 1912, xi, 23.

phlorizinized dogs and demonstrated that even 500 gm. of meat is digested and eliminated as nitrogen and glucose within twelve hours after ingestion. As we have used much smaller amounts of meat and allowed twenty-four hours for elimination, there is no question as to the completeness of digestion, absorption and elimination of the digestive products formed. This is also conclusively shown by the protocols of the experiments, in which, with the exception of chicken egg, the nitrogen and glucose of the ingested material is always seen to be eliminated within twenty-four hours.

The protocols of the feeding experiments accompany this article (Table 6). For the mode of calculation of that portion of the glucose excreted which is ascribable in origin to the proteins ingested, Lusk's method, which is now generally accepted, was employed. Three or more separate experiments were performed in the case of each variety of protein food given. The results of the various experiments usually showed remarkably close agreement (see protocols). It was thus found possible to determine the extent of glucose formation from meat proteins with the same accuracy as that in the case of analytically pure proteins employed in earlier experiments.

TABLE 3.—GLUCOSE FORMED IN METABOLISM BY PROTEIN FOODS

Food	From Raw Material, per Cent.	From Water-Free Material, per Cent.
Beef.....	9.5	38
Rabbit.	11	45
Fish (halibut).....	12	45
Chicken.....	12	48
Chicken egg.....	9.5	36

In Table 3 are recorded the average results of the feeding experiments given in detail in the protocols. It is seen that the amounts of glucose produced from the meats of various origin show no more deviation than might be ascribed to experimental error. These results stand therefore in accord with data previously obtained in this laboratory, which showed that the body proteins of various species of animals all yield approximately like amounts of glucose in metabolism (Janney and Blatherwick).

The reliability of these results for the various meats studied we believe to be scarcely open to question, owing to the careful preliminary experiments alluded to. The same cannot, however, be maintained for the egg experiments, in which larger amounts of material were fed than our later control experiments referred to above. Owing

principally to this fact, in all likelihood a much longer time was required for the sugar and nitrogen arising from them to be excreted than in the case of the meats. The results obtained in this case are perhaps not so dependable as in the meat experiments. They are, however, very regular and do not vary more than the similarly obtained glucose values of the other protein foods. On these grounds they are included with this explanation in our report.

TABLE 4.—GLUCOSE FORMATION FROM PROTEIN FOOD; COMPARATIVE TABLE

	Water Content, per Cent.	Glucose Yield, per Cent.	Amount Equivalent to 100 Gm. Bread, Gm.	Calories per 100 Gm.
Beef, raw.....	74.8	9.5	642	150
Beef, broiled.....	54 †	17.5	348	208
Beef, dried or smoked.....	54.3	21	290	185
Beef, canned or corned.....	51.8	18.2	335	270
Beef, roasted.....	48.2	19.5	313	241
Chicken meat, raw.....	74.5	12	508	197
Chicken meat, roasted.....	59.9	19.2	317	245
Rabbit, raw.....	74.7	11	555	...
Rabbit, broiled.....	61.4†	16.8	363	...
Halibut steak, raw.....	75.4	12	508	124
Halibut steak, fried.....	54.2†	22.3	255	173
Eggs, raw.....	73.7	10.3	592	153
Eggs, boiled.....	73.2	10.51	580	166
Eggs, fried.....	70.4†	11.6	526	160
Ovalbumin*.....	54	113	...
Gelatin*.....	65	94	366
Casein*.....	48	127	...
Corn protein, zein*.....	53	115	...
Wheat protein, gliadin*.....	80	76	...
Flour*.....	92.5
Bread.....	34 †	61	...	277

* Calculation based on water-free material.

† Writers' analysis.

‡ Analyses from Conn. Agric. Exper. Station Report, Sec. 1, Diabetic Foods, 1913.

The results of this series of protein food experiments, though obtained at the cost of considerable effort, are not directly applicable as they stand, however, to the problems of the diabetic's dietary. This is true as they are referable as calculated to raw material, except in the case of the egg feeding. By taking into consideration the loss of water in cooking, it is possible, however, to compute the amount of

glucose which arises in the metabolism of such protein food as served. Such calculations have been made and appear in Table 4. As about one third of the water is usually lost in the culinary preparation, the glucose yields are correspondingly increased. It is apparent that a very considerable amount of glucose arises from meats. Owing chiefly to their higher water content raw, boiled or fried eggs produce but slightly more than one half the sugar which is formed from roast meat. Eggs are therefore to be regarded as a standard article of the diabetic's protein dietary. This experimental observation coincides with the experience of von Noorden with the human diabetic, as this clinician is accustomed to feed eggs in preference to other protein food in order to obtain a decrease in the glycosuria.

In the dietary tables for diabetics compiled by Carl von Noorden various foods are compared in regard to their carbohydrate content to white bread and equivalent values calculated. This method of comparison, as the present article demonstrates, is a rather inexact one, for the additional glucose formed within the organism from the proteins of the foods was not taken into account. In order then to supply a more proper basis for comparison of such foods from this standpoint it is necessary to ascertain the amount of sugar actually arising in the metabolism of bread. To accomplish this a final series of experiments was carried out, some of which have been reported in detail by Mr. Csonka³⁵ from another point of view. On account of its more constant constitution in these experiments, wheat flour was used in preference to bread. The same method of experimentation was employed as previously, with satisfactory results. It could thus be ascertained that flour produced an amount of glucose in metabolism equivalent to 92.5 per cent. of its water-free weight. From the data so obtained it is possible to calculate that the amount of glucose formed from bread in metabolism is about 61 per cent.

We were now finally in a position to calculate the amounts of protein food equivalent from the standpoint of actual glucose formation in the body to bread. These values appear in the last column of Table 4. It is seen that about from 3 to 3.5 parts of cooked meats correspond to one part wheat bread. In view of this fact it follows that rather more care in regard to the protein part of the diabetic's dietary should be exercised than is at present usually deemed necessary. In order to emphasize the marked glycogenetic property of proteins the bread equivalents of various food proteins have been added. Thus gelatin, recommended by von Noorden as a permissible food, produces 65 per cent. glucose within the body, and but 94 parts of gelatin are equivalent to 100 parts of bread. It must be remembered, however,

35. Csonka, F. A.: Jour. Biol. Chem., 1916, xxvi, 327.

that gelatin is eaten in the form of a jelly with a corresponding resulting reduction of the percentage of metabolic glucose formed from it. It is nevertheless certainly no longer to be regarded as a proper food for diabetics.

With regard to the relative usefulness of the various kinds of bread in the diabetic's dietary, the following may here be observed. As nearly as can be at present approximated, the proteins of corn bread yield about 50 per cent. of glucose in metabolism, wheat and rye bread about 66 per cent. The results of the average analyses of Atwater and Bryant are, respectively, for graham (wheat), corn and rye bread, protein, 8.9, 7.9, 11.9 per cent.; carbohydrates, 52.1, 46.3, 35.9 per cent. From this and other data in this article the total percentile sugar yield of these important foodstuffs in metabolism may be estimated as follows: white wheat bread 61, graham wheat 55, corn 50 and rye 44 per cent. From these data it would seem as if rye bread should be preferred for diabetic use. Aside, however, from the fact that Americans as a rule do not relish rye bread, its caloric value is but three fourths that of the other varieties mentioned. Everything considered, then, it seems evident that white wheat bread is least desirable for the diabetic's use, corn bread and other corn-meal preparations most desirable, graham and rye bread occupying a middle position.

7. GLUCOSE FORMATION FROM PROPRIETARY FOODS

So much emphasis has been laid by the physician on the necessity of excluding carbohydrates from the diet of the glycosuric patient that this has become the aim of the manufacturers in preparing diabetic foods. Indeed, it still remains the custom of physicians to recommend at times such special breads and other products on account of their high protein and low carbohydrate content. Many falsifications and misleading statements in regard to the makeup of these foods have, however, been made on the part of their promoters. Analyses of such American commercial products by the state agricultural experiment stations, of German preparations by Magnus-Levy,³⁶ Janney³⁷ and others have already called sufficient attention to such misrepresentations. A study of the actual nutritive value of these preparations to the diabetic, however, is of more importance than the claims made for them commercially. It has been found possible to apply the experimental data previously obtained to these patent diabetic foods and thus to secure a knowledge of their real usefulness to the glycosuric patient. The results of this consideration are collected in Table 5.

36. Magnus-Levy, A.: Berl. klin. Wchnschr., 1910, xlvii, 233.

37. Janney, N. W.: München. med. Wchnschr., 1910, lvii, 2086.

The protein and carbohydrate values used in making these calculations are those compiled by the Connecticut Agricultural Experiment Station³⁸ from scientific investigations of these food products and are said to be regarded as reliable. The percentile amount of glucose produced in the body by these products (third column, Table 5) has been calculated by adding to their carbohydrate content the amount of glucose formed from the protein present, these latter values being taken from our experiments. It has been previously ascertained by the author that casein produces 48 per cent. of glucose. For plasmon and sanatogen, which are casein preparations, this value has accordingly been utilized.

TABLE 5.—GLUCOSE FORMATION FROM PATENT DIABETIC FOODS

	Protein, per Cent.	Carbohy- drate, per Cent.	Glucose Yield in Metabo- lism, per Cent.	Amount Equivalent to 100 Gm. Bread, Gm.
Gildine, Menley & James, New York.....	91.4	1	66	92
Sanatogen, Bauer Chem. Co., Berlin.....	80.1	4.2	61	100
Plasmon, Plasmon Co., London.....	78.7	0	56	109
Diabetic Biscuit, Johnson Educ. Food Co., Boston.....	25.3	59	77	79
40 % Gluten Biscuit, Kellogg Food Co., Mich. ..	35.8	54	79	77
80 % Gluten Biscuit, Kellogg Food Co., Mich. ..	82.4	4.4	63	97

In order to ascertain the total amount of sugar derivable from gluten preparations, it is necessary to ascertain the amount of glucose arising from the wheat proteins. This was done as follows: Of the wheat proteins about 90 per cent. are represented by glutelin and gliadin in the proportion of 10 to 8.4. These two proteins are the chief constituents of gluten. In the absence of actual feeding experiments the amount of metabolic glucose derived from glutelin was calculated as previously done in the case of other proteins, from the amounts of glycogenetic amino-acids obtained from it by hydrolysis.²⁷ The resulting value is 66.3 per cent. Gliadin produces 80 per cent. of glucose in metabolism, as determined experimentally. Accepting that the remaining proteins of the wheat gluten yield about 60 per cent. of glucose under the same circumstances, we can calculate from these data that the wheat gluten gives rise to about 70.5 per cent. of glucose in metabolism. This value has been made use of in compiling the table. It must be borne in mind that the values so calculated are only approximate, owing to the manner in which they are obtained. Thus the method commonly in use for estimating the amount of protein

38. Diabetic Foods, Conn. Agr. Exper. Station, Annual Report, 1913, i, 1.

present in albuminous foods is quite inaccurate. Attention to this has been recently called by the writer.³⁹ Table 5, however, serves forcibly to illustrate the lack of value or indeed positive harmfulness of such commercial products when eaten by the diabetic. It may be remarked that sanatogen, plasmon and glidin, the last a German product identical to that appearing in Table 5, are recommended by von Noorden among foods permissible to all diabetic patients.⁴⁰

A further important fact is also brought out by the data of Table 5. Contrary to the prevailing opinion, the use of food preparations with a high protein and a low carbohydrate content is of not much more advantage to the diabetic than that of others containing much more carbohydrate and less protein. This is well illustrated by comparing the Kellogg Food Company's 40 per cent. gluten biscuit with their 80 per cent. product. Although in the second case the protein has been increased from 35.8 to 82.4 per cent. and the carbohydrates decreased from 54 per cent. to 4.4 per cent., the glucose formed in the metabolism of this product could thereby be reduced from 77 to only 58 per cent. The chief lesson to be drawn from these considerations is obvious. Food products containing high amounts of proteins cannot be properly recommended for the use of diabetics, inasmuch as most of them present no advantages over wheat bread fed in like amount. As these articles are with few exceptions relatively very expensive, and, owing to advertising propaganda, the unsuspecting diabetic is often deluded as to their value, their sale should no longer be encouraged by either physician or layman. A comprehensive list of such diabetic foods has been published, with their protein and carbohydrate content, by the Connecticut Agricultural Experimental Station.³⁸ This may be referred to for determining the utility of diabetic foods other than the few examples quoted in this article.

8. APPLICATION OF RESULTS TO THE DIABETIC DIETARY

The experimental results described in this article were obtained with the aid of the same technic throughout. Optimal conditions for digestion and absorption were maintained for small amounts of protein foods in highly assimilable form which were fed to fasting subjects. Reasons have already been stated for regarding the glucose values as representing the maximal sugar formation from the protein material in each case. It is therefore justifiable to regard the tables given as a general index of the utility of proteins and protein food for the diabetic and to draw comparative conclusions from these data as has been done in the foregoing pages.

39. Janney, N. W.: *Proc. Soc. Exper. Biol. and Med.*, 1916. xiii, 83.

40. Von Noorden, C.: *Die Zuckerkrankheit und ihre Behandlung*, Berlin, 1912, Ed. 6, appended tables.

In actual practice, however, such ideal conditions as the experimental do not exist. The various factors influencing the extent and rate of protein assimilation here become of decided consequence. Among them are the texture of the food served, thoroughness of mastication, presence of substances other than protein in the diet, volume of indigestible material in the intestinal tract, variations in the tolerance to carbohydrates, the effect of exercise and psychic influences. On applying, then, to the diabetic's dietary the results of the researches described in this article, the influence exerted by these factors must be regarded. A very palatable and digestible protein food, though shown to yield much more glucose by our experiments than another example, may possibly, through poorer digestibility and absorption or the fact that these processes take place more slowly in this case, be the cause of less sugar excretion than the second food on their administration to patients. Von Noorden's view that vegetable proteins more favorably influence the glycosuria than does meat, though based on insufficient experimental proof, is, however, susceptible of explanation on these grounds. Vegetable proteins, as we have seen, actually form as much, and in some instances more, glucose in metabolism than do meats, when both these forms of food are fed under optimal conditions. If, however, vegetables are for any reason eaten by diabetics in a form less or more slowly assimilable than a given amount of meat, glucose formation would be correspondingly decreased in the former case. Further exact experiments seem here indicated.

The aim of modern cooking, however, is to render all food, whether animal or vegetable, highly palatable and digestible. The alimentary factors alluded to play in better practice not so great a rôle as might be supposed. With some possible exceptions, these variables would, especially in better households, tend to exert a more similar influence on the course of protein digestion. For this reason the glucose values of the tables in this article are believed to be applicable to the human dietary in a comparative way, even though they may not always represent the precise extent of glucose formation under the special conditions prevailing at the time of their ingestion. Thus, protein foods *A* and *B* may be equivalent to 80 and 60 gm. of bread, respectively, as experimentally determined. Being eaten under mutually the same but less favorable alimentary conditions by a diabetic, each protein might undergo 90 per cent. absorption. Therefore the values in the tables still remain criteria of the relative utility of these proteins. It is to be emphasized, however, that the results of the series of experiments here reported are to be regarded merely as a general gage of the relative adaptability of protein foods to the diabetic dietary.

The Choice of Diet for Diabetics.—The experimental data described in this communication emphasize the fact that large quantities of glu-

TABLE 6.—PROTOCOLS OF FEEDING EXPERIMENTS

Protein Food Administered		Nitrogen Fed, Gm.	Weight of Dog, Gm.	Period, Hr.	Urinary Nitrogen, Gm.	Urinary Glucose, Gm.	G:N	Extra Glucose	
Kind	Amt., Gm.							Amt., Gm.	In Terms of Material Fed, %
Lean beef.....	50	1.66	9.95	24	9.23	32.64	3.54	4.46	8.92
				24	9.12	34.9	3.83		
				24	8.64	29.1	3.37		
				24	6.87	22.22	3.23		
Lean beef.....	35	1.16	7	24	8.58	31.8	3.7	3.3	9.43
				24	5.87	20.7	3.53		
				24	8.19	25.6	3.13		
Lean beef.....	89.6	2.84	8.6	24	8.18	26.79	3.28	8.34	9.30
				24	8.98	23.17	3.13		
				24	7.38	23.57	3.19		
Lean beef.....	108.02	3.5	7	24	5.77	18.64	3.23	9.57	8.86
				24	5.23	16.85	3.24		
				24	4.84	16.26	3.36		
				24	4.76	14.24	2.99		
				24	6.79	20.39	3.01		
				24	4.2	13.86	3.3		
Lean beef.....	91.67	2.97	9.9	24	8.03	29.23	3.64	9.89	10.79
				24	9.88	34.63	3.47		
				24	7.71	27.42	3.55		
Chicken meat.....	134.85	5	10	12	5.12	16.78	3.28	19.14	14.2
				12	4.77	14.52	3.05		
				24	10.89	37.78	3.47		
				24	7.76	24.75	3.19		
Chicken meat.....	128.1	4.75	9.1	24	9.19	28.25	3.07	14.23	11.1
Chicken meat.....	82.93	3.07	6.1	12	3.89	15.27	3.92	10.91	11.86
				12	5.74	19.31	3.37		
				24	8.44	28.73	3.4		
				24	5.57	18.18	3.27		
Chicken meat.....	74.16	2.75	5.9	24	6.27	21.43	3.42	9.48	12.79
Chicken meat.....	74.16	2.75	5.5	24	4.4	15.55	3.53	7.93	10.76
				24	5.98	19.12	3.2		
				24	3.69	12.5	3.39		
Halibut.....	167.8	5	10	12	4.77	16.26	3.41	15.92	9.49
				12	4.16	14.03	3.37		
				24	11.23	37.04	3.3		
Halibut.....	143.1	4.25	8.5	24	2.67	8.03	3.01	13.64	9.54
				24	10.26	31.71	3.09		
				24	7.19	21.58	3		
Halibut.....	63.97	1.9	3.8	24	3.49	10.92	3.13	6.6	10.33
				24	4.73	15.43	3.26		
				24	3.75	11.56	3.09		
Chicken egg.....	176.2	3.7	7.4	12	4.41	16.95	3.85	16.04	9.11
				12	3.92	15.75	4.02		
				24	10.5	40.28	3.83		
				12	3.95	16.95	4.29		
				12	4.31	16.05	3.73		
Chicken egg.....	154.8	3.25	6.5	24	7.82	27.55	3.52	10.1	9.11
				24	8.44	31.25	3.7		
				12	3.31	12.66	3.85		
				12	3.07	10.75	3.5		
Chicken egg.....	390.4	8.2	16.4	24	12.49	40.82	3.3	40.76	10.44
				12	5.53	21.05	3.8		
				24	15.6	61.21	3.93		
				12	4.8	20.13	4.23		

* For protocols of rabbit experiments see Janney, N. W., and Csonka, F. A.: Jour. Biol. Chem., 1915, xxii, 203.

cose are formed within the diabetic organism from food proteins. Evidently the classic severe or strict diet, consisting chiefly of protein, still represents large quantities of sugar-forming material, however carefully carbohydrates are excluded from the articles consumed in such food. It seems, in view of these new results, scarcely a wise procedure to strive to eliminate every gram of carbohydrate from such a diet, inasmuch as nearly two thirds of the proteins fed are found to be converted into glucose in course of metabolism by the diabetic. As it is a matter of clinical experience that large quantities of fats serve to increase both glycosuria and ketonuria, it may be fairly asked what then remains for the diabetic to eat if protein, carbohydrates and fats all contribute to increase the amount of sugar lost to the body in the urine.

This question has indeed been logically answered by Allen, whose well-known treatment has emphasized the good results to be obtained from a complete fast. The rationale of the Allen treatment becomes more evident when one is mindful of the fact that not carbohydrates alone, but all the three great classes of foodstuffs may give rise to increased glucose formation. Thus it becomes apparent that only by total exclusion of all food, a complete rest can be given to the sugar utilizing function of the organism.

The diabetic, however, can not refrain indefinitely from food. How then feed him? In view of the series of experiments here reported it is likely that a diet containing moderate amounts of protein and fat and low amounts of carbohydrate is after all the most judicious one to be employed. It seems that only by very discriminatingly balancing the various advantages and disadvantages of each kind of foodstuff can the proper quantity for a given case be best determined. With the use of the food table giving the equivalents of meats and bread, the amount of protein food in relation to carbohydrates can be easily calculated.

9. SUMMARY

A critical study of diabetes mellitus and phlorizin diabetes has led to the conclusion that glucose formation from protein in both these conditions is essentially the same. It is therefore justifiable to apply the very much more accurate results which can be obtained in phlorizin experiments to the study of human diabetes. By employing a carefully controlled technic it was found possible to quantitatively determine the amount of glucose formed in the organism from ingested proteins. The chief results of previous investigations of the writer and co-workers are collected. They are as follows: Isolated proteins were found to yield large amounts of glucose in metabolism, varying from 48 to 80 per cent. according to the protein examined. Contrary to existing opinions, the animal or vegetable origin of proteins bears no

relationship to their ability to produce glucose in the animal organism, this function being found to be mainly dependent on the amounts of sugar-yielding amino-acids entering into the constitution of these various proteins.

The formation of glucose from body proteins was also studied. It could be shown that body proteins of man and animals yield about 58 per cent. of glucose in metabolism. The nitrogen of these proteins bears about the relation of 3.6 to 1 to the glucose formed from them. This definite establishment of the glucose-nitrogen ratio is of value in the prognosis of diabetes. Cases showing such a high urinary glucose-nitrogen ratio, average 3.4 to 1, are to be regarded as grave. The lower the ratio the more favorable is the prognosis. As the glucose excreted by the fasting diabetic is of protein origin, sugar formation from fat does not take place to any great extent in this disease.

New experiments relative to glucose formation from protein foods are also reported. The amount of glucose originating in the diabetic metabolism from various meats was ascertained with use of the same technic as hitherto. In von Noorden's food tables for diabetics, glucose formation from protein has not been taken into account. By adding the amounts of glucose yielded in metabolism by the proteins of a given food to its carbohydrate content it is possible, however, to ascertain the actual amount of sugar, both set free and formed in the metabolism of such foods. A more accurate table could thus be constructed showing the relative adaptability of protein foods to the diabetic dietary, as compared to equivalent amounts of bread. Finally, various proprietary protein foods were studied in like manner. It was found that such preparations present no advantages over equal amounts of bread when fed to diabetics, as the large amount of protein present leads to the formation of considerable glucose in metabolism.

SOME STUDIES OF A DIURETIC (THEOCIN) *

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In 1913 and 1914 there were published by myself and my associates¹ several studies of the action of diuretics on animals with acute experimental renal lesions. In general, these studies showed that diuretics in acute experimental nephritis were ineffectual or injurious, very often the latter. In 1915 a brief report² was made of observations on the effect of diuretic drugs in patients with chronic nephritis. In a recent Harvey Lecture³ this same subject is touched on. Here it is pointed out that frequently when the kidney is damaged diuretics do not cause a diuresis, or if a diuresis occurs, there may be evidence of marked renal fatigue subsequent to the diuresis. Skepticism has been expressed as to the efficacy of diuretic drugs in cases of nephritis in which the kidney is seriously damaged. In these several studies theocin was used, as well as other diuretics.

During the past winter further study has been made of the action of theocin in patients with acute or chronic nephritis admitted to the medical wards of the Peter Bent Brigham Hospital. The general plan of this study was first to investigate the patients by the usual methods of physical examination, next to study their renal function by several methods and then to place them on a fixed diet for several days preceding and following one or several doses of theocin. During this latter period some patients had the sodium chlorid and nitrogen determined quantitatively in the twenty-four hour amount of urine; in other patients these quantifications were made in two-hour portions of day

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1. Christian: Diuretic Drugs in Acute Experimental Nephritis, *Jour. Am. Med. Assn.*, 1913, lxi, 267. Christian and O'Hare: A Study of the Therapeutic Value of a Diuretic (Theobromin Sodium Salicylate) in Acute Experimental Nephritis, *THE ARCH. INT. MED.*, 1913, xi, 517. Walker and Dawson: The Effect of Diuretic Drugs on the Life of Animals with Severe Acute Nephritis, *ibid.*, xii, 171. Christian: The Effect of Theobromin Sodium Salicylate in Acute Experimental Nephritis as Measured by the Excretion of Phenolsulphonethalein, *ibid.*, 1914, xiv, 829. Fitz: The Immediate Effect of Repeated Doses of Theobromin Sodium Salicylate and Theocin on Renal Function in Acute Experimental Nephritis, *ibid.*, 1914, xiii, 945.

2. Christian, Frothingham, O'Hare and Woods: *Am. Jour. Med. Sc.*, 1915, cli, 666.

3. Christian: *Am. Jour. Med. Sc.*, 1916, cli, 625.

urine and one portion of night urine.† Following the giving of theocin, certain tests of renal function were repeated and contrasted in result with similar tests before the theocin was given. Three types of cases were studied: patients with acute nephritis, patients with chronic nephritis and patients with chronic cardiorenal disease.

ACUTE NEPHRITIS

CASE 1 (P. B. B. H. Med. No. 4159).—A man, aged 27, was admitted to the hospital Feb. 14, 1916, with a diagnosis of acute nephritis. His symptoms had lasted one week, developing one and one-half weeks after a sore throat and cold in the head lasting four days. He suffered from headache and slight edema of the eyelids and feet. There was no edema at the time of the tests. The blood pressure on February 14 was systolic 144, diastolic 100; on the 18th, systolic 140, diastolic 92; on the 22d, systolic 120, diastolic 88; and on the 26th, systolic 112, diastolic 80.

A Wassermann reaction on the blood serum proved negative. Examination of the urine on February 14 showed a trace of albumin and many granular casts and leukocytes. On February 26 there was no albumin, no casts, and only an occasional leukocyte. Phenolsulphonephthalein excretion on February 15 was 60 per cent. in two hours. The blood urea nitrogen on February 15 was 11.25 mg. per 100 c.c. of blood; on the 24th it was 17.5 mg., and on the 28th, 18.5 mg. The index of urea excretion (McLean) on February 24 was 129 per cent., and on the 28th, 71.5 per cent.

TABLE 1.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
2/21-22	530	1.025	0.74	3.92	0.24	1.27
2/22-23	320	1.025	1	3.2	0.35	1.12
2/23-24	475	1.023	0.92	4.37	0.45	2.14
2/24-25	782	1.018	0.66	5.16	0.34	2.66
On February 25 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
2/25-26	1,360	1.014	0.4	5.44	0.31	4.22
2/26-27	389	1.024	1.11	4.32	0.34	1.32
2/27-28	633	1.014	0.68	3.67	0.25	1.58

The diet was approximately 25 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000.

Figure 1 illustrates graphically the daily variations of the amount of urine and the total nitrogen and sodium chlorid, as well as the specific gravity and the percentage concentration of sodium chlorid and nitrogen, with the of three doses of 0.1 gm. each of theocin on one day of the observation. Table 1 gives the results of the urinary analyses.

† It is a pleasure to acknowledge the assistance of Miss Russel and Miss Cate, chemical technicians, in making these numerous quantitations of sodium chlorid and nitrogen.

CASE 2 (P. B. B. H. Med. No. 4245).—A man, aged 45, was admitted to the hospital Feb. 28, 1916, with a diagnosis of acute nephritis. His symptoms had lasted one week, beginning with a cold, lacrimation, headache, slight hacking cough, chilly feelings and pains in the chest. The patient had on entrance no other symptoms except those described above as associated with the onset. Coming to the outdoor department for this condition, he was examined and it was found that he had albumin in his urine and enormous numbers of casts of all varieties. The blood pressure on February 29 was systolic 108, diastolic 62; on the 12th, systolic 120, diastolic 70; on the 24th, systolic 138, diastolic 78; and on April 5, systolic 115, diastolic 82.

A Wasserman reaction on the blood serum proved negative. The urine on February 29 showed a slight trace of albumin and enormous numbers of finely and coarsely granular and hyaline casts, some with epithelial and red blood cells attached. On April 7 there was the slightest possible trace of albumin, no casts, and only an occasional epithelial cell. The phenolsulphonephthalein excretion on February 29 was 50 per cent. in two hours, and on March 18, 45 per cent. in two hours. The blood urea nitrogen on March 1 was 47.5 mg. per 100 c.c. of blood; on the 7th, 13.75 mg.; on the 10th, 12.25 mg.; and on April 10, 17.62 mg. per 100 c.c. of blood. The index of urea excretion (McLean) on March 1 was 35 per cent.; on the 7th, 118 per cent.; on the 10th, 89 per cent., and on April 7, 69 per cent.

TABLE 2.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/ 2/16	810	1.023	1.72	13.93	0.03	0.24
3/ 3/16	473	1.025	1.26	5.96	0.03	0.14
3/ 5/16*	524	1.022	1.18	6.18	0.11	0.58
3/ 6/16	615	1.020	1.1	6.77	0.19	1.17
3/ 7/16	980	1.014	0.44	4.31	0.26	2.55

On March 8 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.

3/ 8/16	900	1.011	0.41	3.69	0.24	2.16
3/ 9/16	300	1.016	0.56	1.68	0.13	0.39
3/10/16	200 lost 829	1.013	0.5	4.15	0.16	1.32
3/11/16	1,225	1.011	0.37	4.53	0.23	2.81
3/12/16	620	1.020	0.82	5.08	0.34	2.11

* The urine for March 4 was discarded because it had been left in a warm room for twenty-four hours.

The diet was approximately 25 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000.

Figure 2 illustrates graphically the daily variations as in Figure 1. Table 2 gives the urinary findings.

CASE 3 (P. B. B. H. Med. No. 4261).—A man, aged 32, was admitted to the hospital March 1, 1916, with a diagnosis of acute nephritis. The symptoms had lasted ten days, developing one month after a tonsillitis with a peritonsillar abscess, followed by pain in some of the patient's joints. There had been slight edema of the face and legs, but there was none at times of tests. The blood pressure on March 4 was systolic 122, diastolic 85; on the 20th, systolic 140,

diastolic 90; on April 9, systolic 128, diastolic 88; and on April 21, systolic 125, diastolic 82.

A Wassermann reaction on the blood serum was negative. The urine on March 2 showed a large trace of albumin and very many red blood cells. On April 28 there was a slight trace of albumin and a moderate number of fine and coarsely granular casts, an occasional cellular cast and epithelial and white blood cell. The phenolsulphonephthalein excretion on March 2 was 36 per cent. in two hours; on April 6, 11 per cent. in two hours, and on April 28, 24 per cent. in two hours. The blood urea nitrogen on March 7 was 45 mg. per 100 c.c. blood; on the 10th, 50.62 mg. per 100 c.c. blood, and on the 28th, 59.37 mg. per 100 c.c. blood. The index of urea excretion (McLean) on March 7 was 3.12 per cent.; on the 10th, 2.48 per cent., and on April 28 it was 7.55 per cent.

TABLE 3.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/ 2/16	958	1.014	0.43	4.12	0.5	4.79
3/ 3/16	168	1.015	0.22	0.37	0.31	0.52
3/ 5/16*	715	1.011	0.21	1.5	0.2	1.43
3/ 6/16	720	1.011	0.37	2.66	0.18	1.3
3/ 7/16	835	1.012	0.21	1.75	0.17	1.42

On March 8 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.

3/ 8/16	1,162	1.010	0.31	3.6	0.21	2.44
3/ 9/16	845	1.010	0.3	2.54	0.15	1.27
3/10/16	918	1.011	0.32	2.94	0.17	1.56
3/11/16	820	1.012	0.31	2.54	0.2	1.64
3/12/16	740	1.012	0.38	2.81	0.19	1.41

* The portion of urine for March 4 was discarded because it had been left in a warm room twenty-four hours.

The diet was approximately 25 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000.

Figure 3 illustrates graphically the daily variations as in Figure 1. Table 3 gives the urinary findings.

CASE 4 (P. B. B. H. Med. No. 4273).—A man, aged 21, was admitted to the hospital March 3, 1916, with a diagnosis of acute nephritis. The trouble had lasted one week, developing after an infection in the right forefinger and thumb. There was slight headache, backache and slight swelling of the ankles, but there was no edema at times of tests. The blood pressure on March 4 was systolic 160, diastolic 90; on the 12th, systolic 130, diastolic 80; on the 24th, systolic 110, diastolic 75; and on April 5, systolic 112, diastolic 68.

A Wassermann reaction on the blood serum was negative. The urine on March 4 showed a trace of albumin, rare granular casts, many red and many white blood cells. On April 7 there was a very rarely granular cast, and an occasional epithelial cell. The phenolsulphonephthalein excretion on March 5 was 50 per cent. in two hours. The blood urea nitrogen on March 11 was 8 mg. per 100 c.c. of blood; on the 20th, 9.75; on the 23d, 11.37; and on April 7, 12.62 mg. per 100 c.c. of blood. The index of urea excretion (McLean) on March 11 was 93.5 per cent.; on the 20th, 71.5 per cent.; on the 23d, 114.0 per cent.; and on April 7, 168.0 per cent.

The diet from March 17 to 23 was approximately 25 gm. protein, 4 gm. sodium chlorid and total calories 2,000. From March 23 to 25 it was approximately 75 gm. protein, 4 gm. sodium chlorid and total calories 2,000.

Figure 4 illustrates graphically the daily variations as in Figure 1. Table 4 gives the urinary findings.

TABLE 4.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/17/16	890	1.013	0.42	3.74	0.18	1.6
3/18/16	1,050	1.012	0.56	5.88	0.15	1.58
3/19/16	920	1.015	0.51	4.69	0.16	1.48
3/20/16	1,358	1.009	0.37	5.03	0.12	1.63

On March 21 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.

3/21/16	1,725	1.008	0.22	3.8	0.14	2.42
3/22/16	915	1.012	0.43	4.49	0.12	1.1
3/23/16	1,317	1.012	0.42	5.51	0.09	1.19
3/24/16	1,317	1.014	0.57	7.51	0.15	1.98
3/25/16	870	1.017	0.74	6.44	0.18	1.56

TABLE 5.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/28/16	533	1.020	1.35	7.47	0.24	1.33
3/29/16	590	1.019	1.38	8.14	0.15	0.89
3/30/16	398	1.019	1.3	5.17	0.11	0.44
3/31/16	386	1.020	1.14	4.4	0.12	0.46

On April 1 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.

4/ 1/16	593	1.020	1.06	6.29	0.23	1.36
4/ 2/16	320	1.020	1.03	3.47	0.24	0.77
4/ 3/16	332	1.022	1.07	3.55	0.68	2.26
4/ 4/16	400	1.023	1.22	4.88	0.17	0.68
4/ 5/16	345	1.020	1	3.45	0.16	0.55

CASE 5 (P. B. B. H. Med. No. 4383).—A man, aged 32, was admitted to the hospital March 23, 1916, with a diagnosis of acute nephritis. The symptoms had lasted two weeks, following a moderately severe cold. There was dark urine with some scalding on urination. There was no edema at the time of the tests. The blood pressure on March 23 was systolic 128, diastolic 85; on April 1,

systolic 110, diastolic 70; on April 5, systolic 120, diastolic 78; and on April 13, systolic 110, diastolic 70.

A Wassermann reaction on the blood serum was negative. The urine on March 23 showed a large trace of albumin and many hyaline and finely granular casts, and but few red blood cells and leukocytes. On April 14 there was a slight trace of albumin, and an occasional granular cast, leukocyte and epithelial cell. The phenolsulphonephthalein excretion on March 28 was 39 per cent. in two hours, and on the 31st, 55 per cent. in two hours. The blood urea nitrogen on March 31 was 19.43 mg. per 100 c.c. blood, and on April 3, 14.68 mg. The index of urea excretion (McLean) on March 31 was 78 per cent., and on April 3, 95.2 per cent.

The diet was approximately 25 gm. protein, 4 gm. sodium chlorid and total calories 2,000. Table 5 gives the urinary findings.

CASE 6 (P. B. B. H. Med. No. 4314)—A man, age 31, was admitted to the hospital March 13, 1916, with a diagnosis of acute nephritis. The symptoms had existed four days without any history of antecedent infection, but with evident caries of teeth. There were severe headache, edema of the face, high-colored urine and chilly sensations, but there was no edema at the time of the tests. The blood pressure on March 13 was systolic 120, diastolic 90; on the 20th, systolic 108, diastolic 60; on the 28th, systolic 108, diastolic 60; and on April 5, systolic 110, diastolic 60.

TABLE 6.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/28/16	1,115	1.018	0.87	9.7	0.31	3.40
3/29/16	1,210	1.015	0.76	9.2	0.24	2.9
3/30/16	940	1.017	0.5	4.7	0.44	4.14
3/31/16	830	1.019	0.93	8.13	0.22	1.83
On April 1 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
4/ 1/16	1,340	1.017	0.71	9.51	0.26	3.48
4/ 2/16	1,122	1.016	0.63	7.07	0.13	1.46
4/ 3/16	770	1.018	1.28	9.86	0.12	0.92
4/ 4/16	1,352	1.015	0.56	7.57	0.22	2.97
4/ 5/16	900	1.014	0.64	5.76	0.13	1.17

A Wassermann reaction on the blood serum was negative. The urine on March 14 showed a very slight trace of albumin, many coarsely granular casts, epithelial cells and leukocytes, and an occasional red blood cell. On April 8 there was no albumin and but few epithelial cells and leukocytes. The phenolsulphonephthalein excretion on March 14 was 56 per cent. in two hours, and on March 31, 64 per cent. in two hours. The blood urea nitrogen on March 15 was 20 mg. per 100 c.c. blood; on the 31st, 15.126 mg., and on April 3, 10.75 mg. The index of urea excretion (McLean) on March 15 was 208 per cent.; on the 31st, 192 per cent., and on April 3, 267 per cent.

The diet was approximately 75 gm. protein, 4 gm. sodium chlorid and total calories 2,000. Table 6 gives the urinary findings.

SUMMARY OF CASES OF ACUTE NEPHRITIS

In six patients with acute nephritis without demonstrable edema at the time of the tests with three doses of 0.1 gm. of theocin a good diuresis was produced in three, a moderate diuresis in two and no diuresis in one. If there occurred a diuresis there was an increased sodium chlorid excretion, though the amount did not increase parallel to the increase in the amount of urine. The excretion of nitrogen sometimes increased, sometimes decreased in the presence of a diuresis; more often it increased, but not as regularly as was the case with sodium chlorid, and the increase in nitrogen did not follow so closely the increase in the amount of urine as did the sodium chlorid.

Forty-eight hours following the diuretic the index of urea excretion (McLean⁴) decreased in three patients and increased in three. Of the six patients, only two had definitely abnormal indexes of urea excretion. One (Case 3) had a very low index. This was a patient who we know to have been free from nephritis several months before these observations, as he was under observation in the hospital for another condition. However, this patient, instead of improving while under observation, progressed into the picture of a subacute to chronic nephritis. The other patient with abnormal index of urea excretion had a high index, which became much higher after the diuresis.

CHRONIC NEPHRITIS

CASE 1 (P. B. B. H. Med. No. 4158)—A man, aged 19, was admitted to the hospital Feb. 14, 1916, with a diagnosis of chronic nephritis. The symptoms had lasted fifteen months, following infection of diphtheria, whooping cough, measles and influenza in childhood. There was edema of the feet and legs, but

TABLE 7.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
2/21-22	978	1.017	0.34	3.33	0.36	3.52
2/22-23	834	1.018	0.38	3.17	0.39	3.25
2/23-24	810	1.016	0.52	4.21	0.31	2.51
2/24-25	718	1.016	0.39	2.8	0.24	1.72

On February 25 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.

2/25-26	920	1.017	0.52	4.78	0.58	5.34
2/26-27	778	1.015	0.55	4.28	0.14	1.09
2/27-28	952	1.012	0.45	4.28	0.11	1.05

4. McLean: Jour. Exper. Med., 1915, xxii, 212, 366.

no edema at the time of the tests. The blood pressure on February 14 was systolic 130, diastolic 110; on the 18th, systolic 140, diastolic 88; on the 22d, systolic 140, diastolic 90; and on the 26th, systolic 120, diastolic 80.

A Wassermann reaction on the blood serum was negative. The urine on February 14 showed a large trace of albumin, many red blood cells, and many finely and coarsely granular, cellular, and hyaline casts. On February 26 there was a large trace of albumin and rare finely granular casts. Many fat droplets were present and an occasional red blood cell and leukocyte. The phenolsulphonephthalein excretion on February 27 was 31 per cent. in two hours. The blood urea nitrogen on February 14 was 25 mg. per 100 c.c. blood; on the 18th, 23.75 mg.; on the 24th, 13 mg., and on the 28th, 20.75 mg. The index of urea excretion (McLean) on February 14 was 16.1 per cent.; on the 18th, 21 per cent.; on the 24th, 40.1 per cent., and on the 28th, 9.5 per cent.

The diet was approximately 25 gm. of protein, 4 gm. sodium chlorid and total calories 2,000. Figure 5 illustrates graphically the daily variations as in Figure 1. Table 7 gives the urinary findings.

TABLE 8.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
2/ 8-9	652	0.55	3.59	0.22	1.43
2/ 9-10	393	0.99	3.89	0.32	1.26
2/10-11	470	0.8	3.76	0.31	1.46

On February 11 theocin was given, 0.3 gm. at 6 a. m. and 9 a. m.

2/11-12	507	0.57	2.89	0.5	2.51
2/12-13	405	0.62	2.51	0.2	0.81
2/13-14	465	0.77	3.58	0.16	0.74
2/14-15	915	0.31	2.84	0.25	2.29
2/15-16	583	0.82	4.78	0.19	1.11
2/16-17	1,046	0.35	3.66	0.21	2.2
2/17-18	768	0.6	4.61	0.26	2
2/18-19	443	0.82	3.68	0.12	0.53

CASE 2 (P. B. B. H. Med. No. 4109).—A woman, aged 45, was admitted to the hospital Feb. 5, 1916, with a diagnosis of chronic nephritis, hypertension, and chronic myocarditis. Her symptoms had lasted four months. She suffered with palpitation, dyspnea, and edema of the legs. There was slight edema at the time of the tests. The blood pressure on February 5 was systolic 250, diastolic 150; on the 10th, systolic 225, diastolic 145; on the 19th, systolic 200, diastolic 135; on the 23d, systolic 225, diastolic 140, and on March 2, systolic 210, diastolic 150.

A Wassermann reaction on the blood serum was negative. The urine on February 5 showed a large trace of albumin, a moderate number of finely granular and hyaline casts, and rarely a red blood cell. On the 28th there was no albumin, but many epithelial and white blood cells. The phenolsulphonephthalein excretion on February 7 was 21 per cent. in two hours, and on the 21st, 28 per cent. in two hours. The blood urea nitrogen on February 7 was 22.25 mg. per 100 c.c. blood, and on the 19th, 23 mg. per 100 c.c. blood. The

index of urea excretion (McLean) on February 7 was 26.5 per cent., and on the 19th, 20.5 per cent.

The diet from February 6 to 12 was approximately 25 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000. From February 12 to 19, approximately 75 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000.

Figure 6 illustrates graphically the daily variations, as in Figure 1. Table 8 gives the urinary findings.

CASE 3 (P. B. B. H. Med. No. 4405).—A man, aged 70, was admitted to the hospital March 27, 1916, with a diagnosis of chronic nephritis, hypertension and syphilis. His symptoms had lasted two weeks. He suffered from edema of the face and legs, fullness in the abdomen, small amount of urine, and dyspnea. There was moderate edema at the time of the tests. The patient died May 4, 1916.

The Wassermann reaction of the blood serum was positive. The blood pressure on March 27 was systolic 195, diastolic 110; on April 5, systolic 160, diastolic 90; on the 17th, systolic 150, diastolic 98, and on the 29th, systolic 170, diastolic 90. The urine on March 27, showed a very large trace of albumin, with very many fine and coarsely granular casts, many leukocytes and red blood cells. On May 4 there was still a large trace of albumin, a moderate number of casts of all descriptions, and a great many red blood cells. The phenol-sulphonaphthalein excretion on March 28, was 17 per cent. in two hours; on the 31st, 14 per cent. in two hours, and on April 24 there was no excretion in two hours. The blood urea nitrogen on March 31, was 48.23 per cent., and on April 3, 45.67 per cent. The index of urea excretion (McLean) on March 31, was 4.35 per cent.; on April 3, 2.38 per cent.

TABLE 9.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
3/28/16	570	1.019	0.96	5.47	0.22	1.25
3/29/16	800	1.020	1.02	8.16	0.2	1.6
3/30/16	1,010	1.021	0.94	9.49	0.22	2.22
3/31/16	820	1.020	0.96	7.87	0.23	1.89
On April 1 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and 6 p. m.						
4/ 1/16	920	1.022	1	9.2	0.23	2.12
4/ 2/16	880	1.022	1.05	9.24	0.28	1.46
4/ 3/16	920	1.019	0.99	9.12	0.37	3.4
4/ 4/16	675	1.021	1.01	6.82	0.19	1.28

The diet from March 28 to April 1, was 800 c.c. milk daily; from April 1 to April 4, approximately 25 gm. protein, 4 gm. sodium chlorid and total calories 2,000.

The urinary findings are given in Table 9.

CASE 4 (P. B. B. H. Med. No. 3537).—A woman, aged 49, was admitted to the hospital Oct. 28, 1915, with a diagnosis of chronic nephritis and hypertension. The symptoms dated back two years. There were dyspnea, edema of the legs, weakness, precordial pain and palpitation. There was slight edema at the time of the tests. The blood pressure on October 28, was systolic 260, diastolic 160; on November 2, systolic 215, diastolic 140; on the 11th, systolic 220, diastolic 135, and on the 29th, systolic 220, diastolic 138.

TABLE 10.—ANALYSES OF TWO-HOUR PORTIONS OF URINE

Time	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
11/12/15						
7 to 9	56	1.012	0.39	0.22	0.1	0.06
9 to 11	80	1.009	0.15	0.12	0.085	0.07
11 to 1	82	1.011	0.33	0.27	0.125	0.1
1 to 3	Lost					
3 to 5	63	1.012	0.28	0.19	0.07	0.05
5 to 7	39	1.018	0.23	0.09	0.1	0.04
7 to 9	97	1.012	0.27	0.26	0.07	0.07
9 to 7	195	1.013	0.33	0.64	0.09	0.18
Total	617	1.79	0.57
11/13/15						
7 to 9	95	1.013	0.18	0.17	0.07	0.07
9 to 11	113	1.007	0.23	0.32	0.05	0.06
11 to 1	34	1.024	0.44	0.16	0.14	0.05
1 to 3	36	1.022	0.4	0.14	0.1	0.04
3 to 5	30	1.026	0.53	0.18	0.12	0.04
5 to 7	23	1.021	0.51	0.12	0.12	0.03
7 to 9	19	1.030	0.69	0.12	0.12	0.02
9 to 7	173	1.018	0.33	0.66	0.11	0.19
Total	523	1.87	0.5

On Nov. 14, 1915, theocin was given, 0.5 gm. at 10 a. m. and at 6 p. m.

11/14/15						
7 to 9	58	1.012	0.03	0.05	0.03	0.05
9 to 11	350	1.008	0.04	0.14	0.15	0.53
11 to 1	258	1.006	0.06	0.16	0.3	0.77
1 to 3	177	1.006	0.11	0.19	0.25	0.44
3 to 5	290	1.008	0.07	0.2	0.2	0.53
5 to 7	135	1.010	0.07	0.1	0.21	0.28
7 to 9	59	1.012	0.1	0.06	0.24	0.14
9 to 7	130	1.019	0.34	0.44	0.23	0.3
Total	457	1.34	3.09
11/15/15						
7 to 9	33	1.016	0.61	0.21	0.16	0.05
9 to 11	42	1.016	0.46	0.19	0.12	0.05
11 to 1	44	1.022	0.54	0.24	0.17	0.03
1 to 3						
3 to 5	34	1.022	0.46	0.16	0.19	0.07
5 to 7	41	1.016	0.34	0.14	0.1	0.04
7 to 9	50	1.015	0.43	0.22	0.07	0.04
9 to 7	163	1.012	0.25	0.41	0.06	0.09
Total	407	1.57	0.42

TABLE 11.—ANALYSES OF TWO-HOUR PORTIONS OF URINE

Time	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
11/1/15						
7 to 9	75	1.019	6.7	0.51	0.25	0.19
9 to 11	91	1.016	5.4	0.49	0.25	0.23
11 to 1	190	1.012	2.1	0.4	0.14	0.27
1 to 3	200	1.013	2.6	0.52	0.14	0.28
3 to 5	120	1.018	5	0.62	0.19	0.23
5 to 7	100	1.015	4.2	0.42	0.16	0.16
7 to 9	210	1.013	4	0.84	0.17	0.36
9 to 7	740	1.012	4	2.96	0.13	0.96
Total	1,726	6.76	2.68
11/2/15						
7 to 9	26	1.024	5	0.13	0.26	0.07
9 to 11	135	1.016	5.4	0.73	0.26	0.35
11 to 1	185	1.013	2.9	0.54	0.11	0.2
1 to 3	235	1.011	2.7	0.64	0.1	0.24
3 to 5	215	1.010	3.1	0.67	0.13	0.28
5 to 7	330	1.011	1.7	0.56	0.09	0.3
7 to 9	268	1.011	2.6	0.6	0.11	0.3
9 to 7	550	1.012	3.6	1.98	0.12	0.66
Total	1,944	5.85	2.4
On Nov. 3, 1915, theocin was given, 0.5 gm. at 10 a. m. and 2 p. m.						
11/3/15						
7 to 9	97	1.016	4.1	0.4	0.22	0.21
9 to 11	390	1.010	1.6	0.62	0.18	0.7
11 to 1	450	1.010	1.4	0.63	0.255	0.35
1 to 3	330	1.010	1.8	0.59	0.215	0.71
3 to 5	240	1.011	2.4	0.68	0.21	0.5
5 to 7	155	1.012	1.3	0.2	0.16	0.25
7 to 9	155	1.012	2.8	0.43	0.18	0.28
9 to 7	450	1.013	2.8	1.26	0.12	0.54
Total	2,267	4.81	3.54
11/4/15						
7 to 9	85	1.019	3.7	0.33	0.2	0.17
9 to 11	110	1.013	4	0.44	0.21	0.23
11 to 1	115	1.015	2.4	0.28	0.18	0.21
1 to 3	220	1.011	1.9	0.43	0.12	0.26
3 to 5	150	1.011	3	0.45	0.12	0.18
5 to 7	155	1.012	2.8	0.43	0.1	0.16
7 to 9	155	1.013	2.4	0.37	0.11	0.17
9 to 7	455	1.014	4.1	1.83	0.1	0.46
Total	1,445	4.51	1.84

The Wassermann reaction on the blood serum was negative. The urine on October 29, showed a slight trace of albumin, a few epithelial cells, no casts and no red blood cells. On December 1, there was no trace of albumin, but many finely granular and hyaline casts, many epithelial cells and a few leukocytes. The phenolsulphonephthalein excretion on November 1, was 52.5 per cent. in two hours; on December 2, 60 per cent. in two hours. The blood urea nitrogen on November 1, was 8.37 mg. per 100 c.c. blood; on the 13th, 10.50 mg., and on the 15th, 16.87 mg. The index of urea excretion (McLean) on November 1, was 120 per cent.; on the 13th, 58.5 per cent., and on the 15th, 23.5 per cent.

The diet was approximately 25 gm. protein, 4 gm. sodium chlorid and total calories 2,000. Figures 7, 8 and 9 illustrate graphically two-hour variations during the day in the amount of urine and in the total nitrogen and sodium chlorid, as well as in its specific gravity and the percentage concentration of sodium chlorid and nitrogen. In addition these same factors are shown in the night portion and the proportionate amount of night to day urine. There also appears the twenty-four hour amount of urine in relation to the twenty-four hour intake of fluid in several days preceding the test day. Figure 8 illustrates these same factors as influenced by two doses of 0.5 gm. each of theocin. Table 10 gives the urinary findings.

CASE 5 (P. B. B. H. Med. No. 3369).—A man, aged 32, was admitted to the hospital Sept. 25, 1915, with a diagnosis of chronic nephritis and hypertension, from which he had suffered four months. He showed symptoms of general edema, dyspnea and failing eyesight. There was very slight edema at the time of the tests. The blood pressure on September 25, was systolic 205, diastolic 135; on October 6, systolic 192, diastolic 135; on October 26, systolic 190, diastolic 120, and on November 10, systolic 210, diastolic 112.

The Wassermann reaction of the blood serum was negative. The urine on September 25, showed a large amount of albumin and many coarsely granular casts, a few hyaline casts containing fat droplets, and many leukocytes. On November 10 there was still a large amount of albumin, numerous hyaline, granular and cellular casts, and numerous leukocytes, with an occasional red blood cell. The phenolsulphonephthalein excretion on September 26 was 36 per cent. in two hours; on October 8, 43 per cent. in two hours, and on October 19, 44 per cent. in two hours. The blood urea nitrogen on September 28 was 23 mg. per 100 c.c. blood; on October 7, 18.12 mg.; on November 2, 29.75 mg., and on November 4, 20 mg. The index of urea excretion (McLean) on September 28 was 21.5 per cent.; on October 7, 45.5 per cent.; on November 2, 20.4 per cent., and on November 4, 16.1 per cent.

The diet was approximately 75 gm. of protein, 4 gm. sodium chlorid, total calories 2,800.

Figures 10, 11 and 12 illustrate graphically two-hour variations during the day in the amount of urine and in the total nitrogen and sodium chlorid, as well as in its specific gravity and the percentage concentration of sodium chlorid and nitrogen. In addition, these same factors are shown in the night portion and the proportionate amount of night to day urine. There also appears the twenty-four hour amount of urine in relation to the twenty-four hour intake of fluid in several days preceding the test day. Figure 11 illustrates these same factors as influenced by two doses of 0.5 gm. each of theocin. Table 11 gives the urinary findings.

SUMMARY OF CASES OF CHRONIC NEPHRITIS

In five patients with chronic nephritis, all except one of whom had some edema at the time of the tests, theocin in varying doses (totals of 0.3 gm., 0.9 gm. and 1 gm.) produced a moderate diuresis in one, a slight diuresis in three and no diuresis in one. In all there was an

increased excretion of sodium chlorid, even in the patient who had no diuresis. The amount of nitrogen excreted was increased in two patients and decreased in three. The index of urea excretion was decreased in three patients, increased in one, while in the fifth the determination was not made close enough to the diuresis to be of any significance. In all of these the index of urea excretion was below normal. In the two patients in which the two hour renal test was carried on during the several days of the testing (Cases 4 and 5, Figs. 7, 8, 9, 10, 11, and 12) this form of test shows a decreased power of concentration during the day on which theocin was given with an almost complete return on the day following to the condition existing prior to giving the theocin.

CHRONIC CARDIORENAL DISEASE

CASE 1 (P. B. B. H. Med. No. 3737).—A man, aged 61, was admitted to the hospital Dec. 6, 1915, with a diagnosis of chronic myocarditis, chronic nephritis, and terminal lobar pneumonia. The symptoms had lasted two years. There were dyspnea, edema, and tenderness over the liver. There was marked edema at the time of the tests. The blood pressure on December 7 was systolic 165, diastolic 125; on the 14th, systolic 160, diastolic 105, and on the 22d, systolic 145, diastolic 110.

The Wassermann reaction on the blood serum was negative. The phenol-sulphonephthalein excretion on December 14 was 30 per cent. in two hours. The blood urea nitrogen on December 7 was 22.75 mg. per 100 c.c. blood. The index of urea excretion (McLean) on December 7 was 19.95 per cent.

TABLE 12.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
4/19/16	520	1.029	1.65	8.58	0.19	0.99
4/20/16	465	1.029	1.74	8.09	0.28	1.3
4/21/16	695	1.025	1.75	12.16	0.48	3.34
On April 22 theocin was given, 0.2 gm. at 6 a. m., 9 a. m. and 12 noon.						
4/22/16	1,980	1.017	0.71	14.06	0.98	19.4
4/23/16	1,200	1.018	0.8	9.6	0.95	11.4
4/24/16	540	1.019	1.31	7.07	0.54	2.92
4/25/16	360	1.020	1.28	4.61	0.18	0.47
4/26/16	300	1.029	1.89	5.67	0.04	0.12

Figure 13 shows the amount of diuresis produced by three doses of 0.5 gm. each of theocin with and without an accompanying digitalis treatment.

CASE 2 (P. B. B. H. Med. No. 4529).—A man, aged 66, was admitted to the hospital April 18, 1916, with a diagnosis of chronic myocarditis and auricular fibrillation. The symptoms had lasted thirteen months. There were dyspnea and edema of the legs. There was marked edema at the time of the tests. The patient died May 17, 1916. The blood pressure on April 18 was

systolic 125, diastolic 85; on the 26th, systolic 140, diastolic 100; on the 29th, systolic 130, diastolic 90, and on May 5, systolic 120, diastolic 100.

The Wassermann reaction on the blood serum was negative. The urine on April 18 showed a slight trace of albumin and a moderate number of hyaline and finely granular casts. On May 4 there was the slightest possible trace of albumin and a moderate number of hyaline and finely granular casts. The phenolsulphonephthalein excretion on April 18 was 17 per cent. in two hours; on the 25th, 19 per cent. in two hours. The blood urea nitrogen on April 21 was 35.64 mg. per 100 c.c. blood, and on the 24th, 21.67 mg. The index of urea excretion (McLean) on April 21 was 72.6 per cent., and on the 24th 88.5 per cent.

The diet was 800 c.c. milk daily.

Figure 14 illustrates graphically the daily variation as in Figure 1. Table 12 gives the urinary findings.

TABLE 13.—ANALYSES OF TWENTY-FOUR HOUR AMOUNT OF URINE

Date	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
4/16/16	840	1.023	0.98	8.23	0.98	8.23
4/17/16	845	1.024	1.19	10.06	0.94	7.94
4/18/16	606	1.024	1.13	6.85	0.91	5.52
On April 19 theocin was given, 0.1 gm. at 10 a. m., 2 p. m. and at 6 p. m.						
4/19/16	1,153	1.021	0.82	9.46	1.1	12.68
4/20/16	650	1.025	0.88	5.72	1.09	7.09
4/21/16	870	1.023	1.06	9.22	1.05	9.14
4/22/16	730	1.023	1.04	7.59	1	7.3
4/23/16	1,215	1.023	1.19	14.46	0.94	11.42
On April 24 theocin was given, 0.3 gm. at 6 a. m. and at 10 a. m.						
4/24/16	1,520	1.018	0.64	9.73	1.12	17.02
4/25/16	1,700	1.014	0.59	10.03	0.84	14.28
4/26/16	1,851	1.014	0.57	7.13	0.48	6.01
4/27/16	1,562	1.013	0.58	9.06	0.46	7.19
4/28/16	635	1.020	0.95	6.03	0.45	2.86

CASE 3 (P. B. B. H. Med. No. 4414).—A man, aged 41, was admitted to the hospital March 28, 1916, with a diagnosis of syphilitic aortitis, dilatation of arch of aorta, aortic insufficiency and chronic nephritis. The symptoms had lasted three years. The patient complained of dyspnea and edema of legs. There was edema at the time of the tests. The blood pressure on April 13 was systolic 138, diastolic 50.

The Wassermann reaction on the blood serum was positive. The urine on April 28 showed the slightest possible trace of albumin and a few hyaline and granular casts, and on the 30th the slightest possible trace of albumin and an occasional hyaline cast. The phenolsulphonephthalein excretion on April 18 was 37 per cent.; on the 21st, 38 per cent., and on the 26th, 34 per cent. The blood urea nitrogen on April 18 was 25.86 mg. per 100 c.c. blood; on the 21st, 21.90 mg., and on the 26th, 18.40 mg. The index of urea excretion

TABLE 14.—ANALYSES OF TWO-HOUR PORTIONS OF URINE

Time	C.c. Volume,	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
12/13/15 7 to 9
9 to 11	42	1.44	0.61	0.4	0.17
11 to 1	38	1.024	0.9	0.34	0.4	0.15
1 to 3	31	1.026	0.66	0.21	0.38	0.11
3 to 5	66	1.027	1.09	0.72	0.63	0.42
5 to 7	51	1.025	1.1	0.56	0.66	0.34
7 to 9	38	1.026	1.08	0.41	0.72	0.27
9 to 7	139	1.028	1.34	1.86	0.4	0.56
Total	405	4.71	2.02
12/14/15 7 to 9	42	1.022	1.36	0.57	0.36	0.15
9 to 11	16	1.032	0.92	0.15	0.4	0.06
11 to 1	43	1.026	0.62	0.27	0.4	0.17
1 to 3	44	1.028	0.96	0.42	0.42	0.19
3 to 5	47	1.024	0.97	0.46	0.55	0.36
5 to 7 }	85	1.026	1.44	1.22	0.43	0.36
7 to 9 }						
9 to 7	12	1.030	0.43	0.05	0.4	0.05
Total	289	3.14	1.34
12/15/15 7 to 9	163	1.022	1.17	1.91	0.44	0.72
9 to 11	66	1.022	1.01	0.67	0.56	0.37
11 to 1	34	1.028	1.1	0.37	0.78	0.27
1 to 3	54	1.023	0.95	0.51	0.76	0.41
3 to 5	71	1.021	0.72	0.51	0.85	0.6
5 to 7	36	1.028	1.04	0.37	0.74	0.27
7 to 9 }	282	1.022	0.61	1.4	0.92	2.59
9 to 7 }						
Total	706	5.74	5.23
On Dec. 16, 1915, theocin was given, 0.3 gm. at 6 a. m., 9 a. m. and 12 noon.						
12/16/15 7 to 9	448	1.012	0.1	0.45	0.86	3.85
9 to 11	620	1.009	0.08	0.5	0.59	3.66
11 to 1	810	1.009	0.04	0.32	0.52	4.21
1 to 3	550	1.008	0.06	0.33	0.47	2.59
3 to 5	630	1.006	0.06	0.39	0.4	2.52
5 to 7	270	1.010	0.07	0.19	0.39	1.05
7 to 9	230	1.010	0.1	0.23	0.33	0.76
9 to 7	590	1.014	0.16	0.94	0.41	2.42
Total	4,148	3.35	21.06

TABLE 14.—ANALYSES OF TWO-HOUR PORTIONS OF URINE—(Continued)

Time	Volume, C.c	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
12/17/15 7 to 9	52	1.017	0.3	0.16	0.32	0.17
9 to 11	7	0.41	0.03	0.2	0.01
11 to 1 } 1 to 3 }	120	1.022	0.43	0.52	0.29	0.35
3 to 5	53	1.023	1.04	0.55	0.32	0.17
5 to 7	38	1.022	0.86	0.33	0.3	0.11
7 to 9	55	1.024	0.39	0.22	0.25	0.14
9 to 7	89	1.024	0.48	0.43	0.27	0.24
Total	414	2.24	1.19

(McLean) on April 18 was 48.2 per cent.; on the 21st, 36.3 per cent., and on the 26th, 35.2 per cent.

The diet from April 14 to 24 was the general house diet. From April 25 to 28 it was approximately 75 gm. protein, 4 gm. sodium chlorid and total calories 2,000. Table 13 gives the urinary findings.

CASE 4 (P. B. B. H. Med. No. 3777).—A man, aged 20, was admitted to the hospital Dec. 11, 1915, with a diagnosis of chronic pericarditis, ascites, and possibly adherent pericardium, the symptoms of which had lasted two months. He complained of dyspnea, edema of the legs and abdomen, with ascites. There was marked edema at the time of the tests. The blood pressure on December 11 was systolic 100, diastolic not obtained; on the 14th, systolic 128, diastolic 116, and on January 13, systolic 118, diastolic 100.

The Wassermann reaction on the blood serum was negative. The urine on December 11 showed slight trace of albumin with frequent hyaline and granular casts and rare red blood cells; on January 16 there was the slightest possible trace of albumin with a few leukocytes, no red blood cells and no casts. The phenolsulphonephthalein excretion on December 21 was 50 per cent. in two hours. The blood urea nitrogen on December 13 was 12.12 mg. per 100 c.c. of blood; on the 17th, 9.12 mg.; and on January 8, 12.50 mg. The index of urea excretion on December 13 was 257.5 per cent.; on the 17th, 22.7 per cent., and on January 8, 176 per cent.

The diet was soft solids.

Figures 15, 16 and 17 illustrate graphically the two-hour variations during the day in the amount of urine and in the total nitrogen and sodium chlorid, as well as in its specific gravity and the percentage concentration of sodium chlorid and nitrogen. In addition these same factors are shown in the night portion and the proportionate amount of night to day urine. There also appears the twenty-four hour amount of urine in relation to the twenty-four hour intake of fluid in several days preceding the test day. Figure 16 illustrates these same factors as influenced by three doses of theocin of 0.3 gm. each. Table 14 gives the urinary findings.

CASE 5 (P. B. B. H. Med. No. 3337).—A man, aged 27, was admitted to the hospital Sept. 14, 1915, with a diagnosis of chronic cardiac valvular disease with mitral stenosis and insufficiency and chronic myocarditis and syphilis, the symptoms having lasted thirteen months. The patient complained of

TABLE 15.—ANALYSES OF TWO-HOUR PORTIONS OF URINE

Time	Volume, C.c.	Sp. Gr.	Nitrogen		Chlorid	
			Per Cent.	Grams	Per Cent.	Grams
11/14/15 7 to 9	64	1.026	0.96	0.61	1.05	0.67
9 to 11	92	1.020	0.21	0.19	0.64	0.59
11 to 1	250	1.008	0.12	0.3	0.17	0.43
1 to 3	285	1.010	0.26	0.74	0.17	0.49
3 to 7	175	1.019	0.64	1.12	0.33	0.58
7 to 9	70	1.026	0.94	0.66	0.37	0.26
9 to 7	200	1.026	1.46	2.92	0.37	0.74
Total	1,136	6.54	3.76
11/15/15 7 to 9	85	1.023	0.7	0.6	0.67	0.57
9 to 11	81	1.017	0.55	0.45	0.55	0.45
11 to 1	225	1.015	0.34	0.77	0.56	1.16
1 to 3	465	1.012	0.18	0.84	0.24	1.12
3 to 5	152	1.013	0.44	0.67	0.37	0.56
5 to 7	69	1.022	0.78	0.54	0.54	0.37
7 to 9	332	1.011	0.27	0.9	0.14	0.47
9 to 7	340	1.015	0.45	1.53	0.25	0.85
Total	1,749	6.3	5.55
On Nov. 16, 1915, theocin was given, 0.5 gm. at 10 a. m. and 2 p. m.						
11/16/15 7 to 9	85	1.016	0.54	0.46	0.4	0.34
9 to 11	48	1.027	0.83	0.4	0.845	0.41
11 to 1	83	1.025	0.75	0.61	0.98	0.81
1 to 3	183	1.017	0.57	1.04	0.47	0.86
3 to 5	330	1.010	0.28	0.92	0.44	1.45
5 to 7	485	1.010	0.07	0.32	0.25	1.21
7 to 9	248	1.015	0.3	0.74	0.4	0.99
9 to 7	248	1.023	0.76	1.69	0.2	0.5
Total	1,710	6.18	6.57
11/17/15 7 to 11	680	1.007	0.06	0.41	0.03	0.2
11 to 1	289	1.009	0.28	0.81	0.07	0.19
1 to 3	245	1.010	0.31	0.76	0.11	0.27
3 to 5	202	1.009	0.27	0.71	0.1	0.26
5 to 7	69	1.021	1.11	0.77	0.155	0.11
7 to 9	60	1.022	0.81	0.49	0.22	0.13
9 to 7	178	1.024	1.44	2.56	0.13	0.23
Total	1,783	6.51	1.89

TABLE 1. SUMMARY OF DATA FOR THE FIRST TWO YEARS									
STATION	DATE	TIME	WIND DIRECTION	WIND SPEED	WAVE DIRECTION	WAVE PERIOD	WAVE HEIGHT	WAVE LENGTH	WAVE ENERGY
STATION 1	1960-01-01	08:00	090	12	090	8	1.5	120	1.5
	1960-01-01	12:00	090	15	090	10	2.0	150	2.0
	1960-01-01	16:00	090	18	090	12	2.5	180	2.5
	1960-01-01	20:00	090	20	090	14	3.0	210	3.0
	1960-01-01	24:00	090	22	090	16	3.5	240	3.5
	1960-01-01	28:00	090	24	090	18	4.0	270	4.0
STATION 2	1960-01-02	02:00	090	26	090	20	4.5	300	4.5
	1960-01-02	06:00	090	28	090	22	5.0	330	5.0
	1960-01-02	10:00	090	30	090	24	5.5	360	5.5
	1960-01-02	14:00	090	32	090	26	6.0	390	6.0
	1960-01-02	18:00	090	34	090	28	6.5	420	6.5
	1960-01-02	22:00	090	36	090	30	7.0	450	7.0
STATION 3	1960-01-03	00:00	090	38	090	32	7.5	480	7.5
	1960-01-03	04:00	090	40	090	34	8.0	510	8.0
	1960-01-03	08:00	090	42	090	36	8.5	540	8.5
	1960-01-03	12:00	090	44	090	38	9.0	570	9.0
	1960-01-03	16:00	090	46	090	40	9.5	600	9.5
	1960-01-03	20:00	090	48	090	42	10.0	630	10.0
STATION 4	1960-01-04	02:00	090	50	090	44	10.5	660	10.5
	1960-01-04	06:00	090	52	090	46	11.0	690	11.0
	1960-01-04	10:00	090	54	090	48	11.5	720	11.5
	1960-01-04	14:00	090	56	090	50	12.0	750	12.0
	1960-01-04	18:00	090	58	090	52	12.5	780	12.5
	1960-01-04	22:00	090	60	090	54	13.0	810	13.0
STATION 5	1960-01-05	00:00	090	62	090	56	13.5	840	13.5
	1960-01-05	04:00	090	64	090	58	14.0	870	14.0
	1960-01-05	08:00	090	66	090	60	14.5	900	14.5
	1960-01-05	12:00	090	68	090	62	15.0	930	15.0
	1960-01-05	16:00	090	70	090	64	15.5	960	15.5
	1960-01-05	20:00	090	72	090	66	16.0	990	16.0
STATION 6	1960-01-06	02:00	090	74	090	68	16.5	1020	16.5
	1960-01-06	06:00	090	76	090	70	17.0	1050	17.0
	1960-01-06	10:00	090	78	090	72	17.5	1080	17.5
	1960-01-06	14:00	090	80	090	74	18.0	1110	18.0
	1960-01-06	18:00	090	82	090	76	18.5	1140	18.5
	1960-01-06	22:00	090	84	090	78	19.0	1170	19.0
STATION 7	1960-01-07	00:00	090	86	090	80	19.5	1200	19.5
	1960-01-07	04:00	090	88	090	82	20.0	1230	20.0
	1960-01-07	08:00	090	90	090	84	20.5	1260	20.5
	1960-01-07	12:00	090	92	090	86	21.0	1290	21.0
	1960-01-07	16:00	090	94	090	88	21.5	1320	21.5
	1960-01-07	20:00	090	96	090	90	22.0	1350	22.0
STATION 8	1960-01-08	02:00	090	98	090	92	22.5	1380	22.5
	1960-01-08	06:00	090	100	090	94	23.0	1410	23.0
	1960-01-08	10:00	090	102	090	96	23.5	1440	23.5
	1960-01-08	14:00	090	104	090	98	24.0	1470	24.0
	1960-01-08	18:00	090	106	090	100	24.5	1500	24.5
	1960-01-08	22:00	090	108	090	102	25.0	1530	25.0
STATION 9	1960-01-09	00:00	090	110	090	104	25.5	1560	25.5
	1960-01-09	04:00	090	112	090	106	26.0	1590	26.0
	1960-01-09	08:00	090	114	090	108	26.5	1620	26.5
	1960-01-09	12:00	090	116	090	110	27.0	1650	27.0
	1960-01-09	16:00	090	118	090	112	27.5	1680	27.5
	1960-01-09	20:00	090	120	090	114	28.0	1710	28.0
STATION 10	1960-01-10	02:00	090	122	090	116	28.5	1740	28.5
	1960-01-10	06:00	090	124	090	118	29.0	1770	29.0
	1960-01-10	10:00	090	126	090	120	29.5	1800	29.5
	1960-01-10	14:00	090	128	090	122	30.0	1830	30.0
	1960-01-10	18:00	090	130	090	124	30.5	1860	30.5
	1960-01-10	22:00	090	132	090	126	31.0	1890	31.0
STATION 11	1960-01-11	00:00	090	134	090	128	31.5	1920	31.5
	1960-01-11	04:00	090	136	090	130	32.0	1950	32.0
	1960-01-11	08:00	090	138	090	132	32.5	1980	32.5
	1960-01-11	12:00	090	140	090	134	33.0	2010	33.0
	1960-01-11	16:00	090	142	090	136	33.5	2040	33.5
	1960-01-11	20:00	090	144	090	138	34.0	2070	34.0
STATION 12	1960-01-12	02:00	090	146	090	140	34.5	2100	34.5
	1960-01-12	06:00	090	148	090	142	35.0	2130	35.0
	1960-01-12	10:00	090	150	090	144	35.5	2160	35.5
	1960-01-12	14:00	090	152	090	146	36.0	2190	36.0
	1960-01-12	18:00	090	154	090	148	36.5	2220	36.5
	1960-01-12	22:00	090	156	090	150	37.0	2250	37.0
STATION 13	1960-01-13	00:00	090	158	090	152	37.5	2280	37.5
	1960-01-13	04:00	090	160	090	154	38.0	2310	38.0
	1960-01-13	08:00	090	162	090	156	38.5	2340	38.5
	1960-01-13	12:00	090	164	090	158	39.0	2370	39.0
	1960-01-13	16:00	090	166	090	160	39.5	2400	39.5
	1960-01-13	20:00	090	168	090	162	40.0	2430	40.0
STATION 14	1960-01-14	02:00	090	170	090	164	40.5	2460	40.5
	1960-01-14	06:00	090	172	090	166	41.0	2490	41.0
	1960-01-14	10:00	090	174	090	168	41.5	2520	41.5
	1960-01-14	14:00	090	176	090	170	42.0	2550	42.0
	1960-01-14	18:00	090	178	090	172	42.5	2580	42.5
	1960-01-14	22:00	090	180	090	174	43.0	2610	43.0
STATION 15	1960-01-15	00:00	090	182	090	176	43.5	2640	43.5
	1960-01-15	04:00	090	184	090	178	44.0	2670	44.0
	1960-01-15	08:00	090	186	090	180	44.5	2700	44.5
	1960-01-15	12:00	090	188	090	182	45.0	2730	45.0
	1960-01-15	16:00	090	190	090	184	45.5	2760	45.5
	1960-01-15	20:00	090	192	090	186	46.0	2790	46.0
STATION 16	1960-01-16	02:00	090	194	090	188	46.5	2820	46.5
	1960-01-16	06:00	090	196	090	190	47.0	2850	47.0
	1960-01-16	10:00	090	198	090	192	47.5	2880	47.5
	1960-01-16	14:00	090	200	090	194	48.0	2910	48.0
	1960-01-16	18:00	090	202	090	196	48.5	2940	48.5
	1960-01-16	22:00	090	204	090	198	49.0	2970	49.0
STATION 17	1960-01-17	00:00	090	206	090	200	49.5	3000	49.5
	1960-01-17	04:00	090	208	090	202	50.0	3030	50.0
	1960-01-17	08:00	090	210	090	204	50.5	3060	50.5
	1960-01-17	12:00	090	212	090	206	51.0	3090	51.0
	1960-01-17	16:00	090	214	090	208	51.5	3120	51.5
	1960-01-17	20:00	090	216	090	210	52.0	3150	52.0
STATION 18	1960-01-18	02:00	090	218	090	212	52.5	3180	52.5
	1960-01-18	06:00	090	220	090	214	53.0	3210	53.0
	1960-01-18	10:00	090	222	090	216	53.5	3240	53.5
	1960-01-18	14:00	090	224	090	218	54.0	3270	54.0
	1960-01-18	18:00	090	226	090	220	54.5	3300	54.5
	1960-01-18	22:00	090	228	090	222	55.0	3330	55.0
STATION 19	1960-01-19	00:00	090	230	090	224	55.5	3360	55.5
	1960-01-19	04:00	090	232	090	226	56.0	3390	56.0
	1960-01-19	08:00	090	234	090	228	56.5	3420	56.5
	1960-01-19	12:00	090	236	090	230	57.0	3450	57.0
	1960-01-19	16:00	090	238	090	232	57.5	3480	57.5
	1960-01-19	20:00	090	240	090	234	58.0	3510	58.0
STATION 20	1960-01-20	02:00	090	242	090	236	58.5	3540	58.5
	1960-01-20	06:00	090	244	090	238	59.0	3570	59.0
	1960-01-20	10:00	090	246	090	240	59.5	3600	59.5
	1960-01-20	14:00	090	248	090	242	60.0	3630	60.0
	1960-01-20	18:00	090	250	090	244	60.5	3660	60.5
	1960-01-20	22:00	090	252	090	246	61.0	3690	61.0
STATION 21	1960-01-21	00:00	090	254	090	248	61.5	3720	61.5
	1960-01-21	04:00	090	256	090	250	62.0	3750	62.0

dizziness and dyspnea. There was edema at the time of the tests. The patient died Jan. 2, 1916. The blood pressure on September 14 was systolic 105, diastolic 75; on the 24th, systolic 110, diastolic 90.

The Wassermann reaction on the blood serum was positive. The urine on September 14 showed a slight trace of albumin, with frequent hyaline and granular casts. On November 19 there was a slight trace of albumin, but no casts and but few leukocytes. The phenolsulphonephthalein excretion on September 21 was 63 per cent. in two hours. The blood urea nitrogen on November 15 was 20.62 mg. per 100 c.c. of blood, and on the 17th, 35 mg. The index of urea excretion on November 15 was 102 per cent., and on the 17th, 68 per cent.

The diet was approximately 75 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000. Table 15 gives the urinary findings.

CASE 6 (P. B. B. H. Med. No. 3602).—A man, aged 64, was admitted to the hospital Nov. 11, 1915, with a diagnosis of hypertension, arteriosclerosis and cerebral hemorrhage. It had been twenty-four hours since the onset of the hemiplegia. There was dizziness, hemiplegia, but no edema at the time of the tests. The blood pressure on November 12 was systolic 182, diastolic 98; on the 19th, systolic 150, diastolic 80; on the 29th, systolic 165, diastolic 95, and on December 8, systolic 155, diastolic 85.

The Wassermann reaction of the blood serum was negative. The urine on November 11 showed no albumin and no casts. The same condition existed on December 7. The phenolsulphonephthalein excretion on November 11 was 84 per cent. in two hours, and on the 18th, 65 per cent. in two hours. The blood urea nitrogen on November 19 was 30 mg. per 100 c.c. blood; on the 30th, 12.75 mg., and on December 2, 12.25 mg. The index of urea excretion on November 19 was 635 per cent; on the 30th, 132.5 per cent., and on December 2, 180 per cent.

The diet was approximately 75 gm. of protein, 4 gm. of sodium chlorid and total calories 2,000. The urinary findings are given in Table 16.

SUMMARY OF CASES OF CHRONIC CARDIORENAL DISEASES

In six patients with chronic cardiorenal disease theocin in varying doses (totals of 0.3 gm., 0.6 gm., 0.9 gm., 1 gm. and 1.5 gm.) produced a marked diuresis in four and no diuresis in two. In the patients who had no diuresis there was no edema present at the time of the tests and during that period there were no signs of cardiac decompensation. In one of the four patients with marked diuresis no quantitations of nitrogen and sodium chlorid were made. In the other three there was a markedly increased excretion of sodium chlorid, while in two the nitrogen excretion was slightly increased, and in one it was decreased. In the two patients without diuresis sodium chlorid excretion was slightly increased in one, slightly decreased in the other, while nitrogen excretion was unchanged in one and slightly decreased in the other. In the three patients with marked diuresis in which the index of urea excretion was determined, one showed a slight increase, one a slight decrease and one a strikingly large decrease. In the two patients with no diuresis one showed an increased and one a decreased index. One patient in this series had a high index of urea excretion and one an index moderately, though definitely below normal. In the others the

indexes were within normal limits. In the three patients (Case 4, Figures 15, 16 and 17, and Cases 5 and 6) in whom the two-hour renal test was carried out on the several days before and after giving theocin, this test showed very little difference in the figures on days preceding and following the theocin.

COMMENT

In this series of patients it is seen that theocin has no constant diuretic action. In patients with little or no demonstrable edema theocin may produce a moderate degree of diuresis (expressed roughly as good in three patients, moderate in three and slight in three) or it may produce no diuresis (four patients). In none of our cases of pure nephritis was there any very great amount of edema at the time the tests were made. In four cardio-renal cases, however, there was a very considerable degree of edema and in these a much greater diuresis was produced by theocin. When a diuresis occurred almost always sodium chloride excretion was increased, but the increase was not parallel to the increase in fluid, though usually the increase in excretion was most marked in those patients in whom occurred the greatest increase in urine output. Sometimes with rather small increases in urine output, sodium chloride excretion was considerably increased. In contrast to sodium chloride, nitrogen excretion was increased less frequently and usually to a less degree. In half of the cases studied nitrogen excretion decreased after giving theocin. Even in patients with a marked diuresis nitrogen excretion might be but little increased or even decreased.

If we consider the question of the therapeutic efficiency of theocin as a diuretic in the light of the above results we would be justified to express skepticism of its value in patients with relatively little demonstrable edema. In the first place an increased urine output is not constant after theocin, though it often occurs. If we give a diuretic to a patient with acute or chronic nephritis having only moderate edema, what might be considered to be the therapeutic effect we are seeking? In such a case the edema in itself is rarely doing much harm. So to remove a large amount of fluid, even were that the result from giving the diuretic, would not in itself be of much therapeutic value. Very likely the patient is toxic and shows signs of uremia. In such an event we might seek by a diuretic to increase elimination through the kidney. Theocin in these cases of ours caused usually an increased elimination of sodium chloride and water, but we have no evidence that sodium chloride retention is harmful unless it is a factor in the production of a disturbing edema. There is more evidence that nitrogenous substances of some kind are toxic, but, as we have seen, nitrogen elimination is

much less constantly increased by theocin and quite often is actually decreased. So, from this point of view we might question the therapeutic efficiency of theocin in cases of nephritis with moderate amounts of edema. Perhaps we can assume that the reason for using a diuretic in this type of case is to increase renal efficiency, to stimulate the kidney to increased work. Measured by water or sodium chlorid output, theocin might be said to accomplish this; measured by nitrogen elimination, function is little improved, often is made worse. Renal efficiency, as measured by the index of urea excretion in cases of acute or chronic nephritis, we have found in our cases to be more often decreased than increased after using theocin, so that the evidence here is against rather than in favor of an increase in renal efficiency from the use of theocin.

Now if we turn to cases in which there is a large element of cardiac insufficiency, we have found that theocin very commonly, especially when used in combination with digitalis, causes an active diuresis, especially in patients with marked edema. In them salt output usually is markedly increased. On the other hand, nitrogen excretion often is but little increased, sometimes actually decreased. In these patients edema is a troublesome symptom. To remove it helps the patient. Theocin is effective in producing a large diuresis and so decreases edema and in this sense is therapeutically efficient. These patients, as a rule, are not toxic and removal of nitrogenous substances is not what is sought from theocin. Even in cases of this group a marked diuresis from theocin is often followed by a drop in the index of urea excretion, suggesting that following great renal activity comes a period of depressed renal function. If this is true, then an intermittent dosage with theocin with intervening periods in which no diuretic is given is probably the best procedure to follow with cases of the cardiorenal group having considerable or marked edema. In a very considerable number of patients with cardiorenal disease we have found theocin to be effective in this sense, used in this way, so that our observations here reported on a few patients with cardiorenal edema in which sodium chlorid and nitrogen elimination and the index of urea excretion were studied are in accord, so far as the effectiveness of theocin in producing diuresis is concerned, with our observations on a number of patients in whom these detailed studies were not made.

The study here reported is of relatively few cases and of but one diuretic (theocin). This being the case, it must be realized that far-reaching conclusions are unjustified. Those that have been drawn should be regarded as merely suggestive. They are, however, quite in

accord with the view previously expressed by myself with regard to diuretics, views based on animal experimentation and various methods of clinical observation.

SUMMARY

A fairly complete study of a small group of patients with acute nephritis or chronic nephritis or cardiorenal disease indicates that theocin in patients with slight or no edema has little or no therapeutic value, inasmuch as diuresis is not constantly produced, elimination of nitrogenous substances quite often is slightly if at all increased and renal function is frequently decreased after giving theocin. In cardiorenal cases with marked edema theocin is of therapeutic value, because it produces, especially in conjunction with digitalis, an active diuresis with increased sodium chlorid elimination, which decreases edema, a troublesome feature in these cases. Inasmuch as there is evidence that following an active diuresis renal function is depressed, an intermittent usage of theocin seems preferable to a continuous usage in cardiorenal cases with edema.

Peter Bent Brigham Hospital.

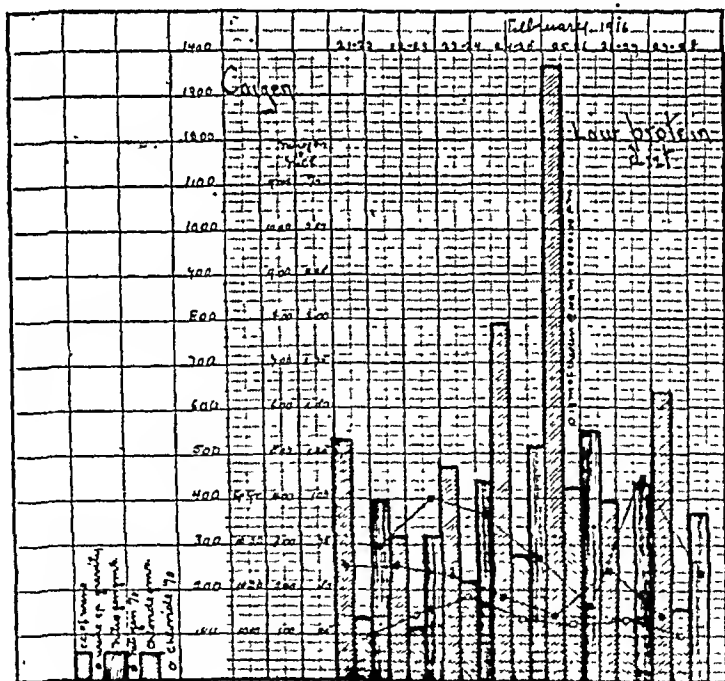


Fig. 1.—Acute nephritis, Case 1. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On February 25 the patient received three doses of 0.1 gm. each of theocin.

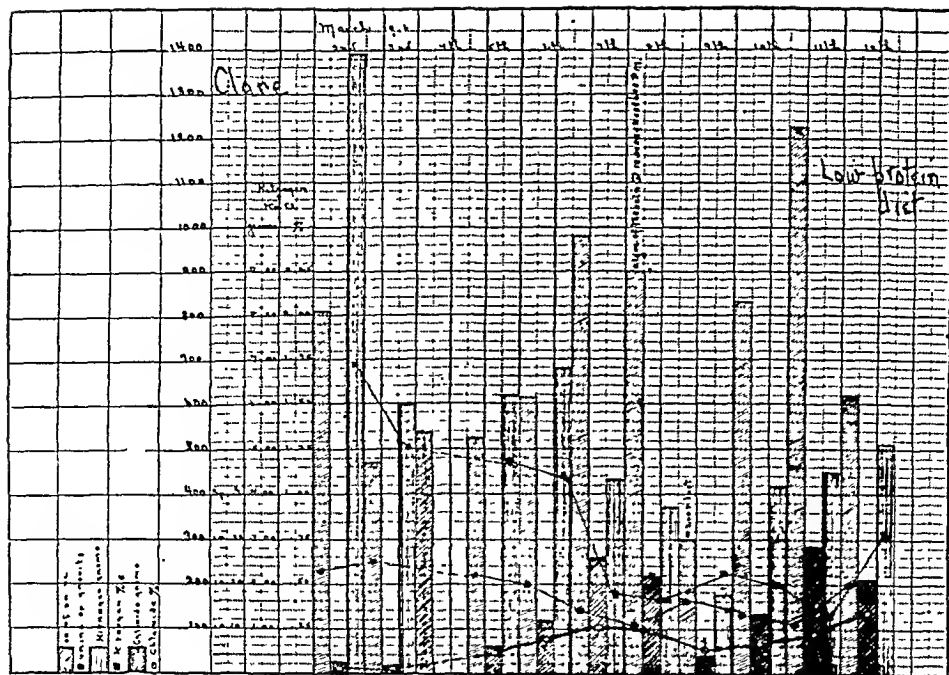


Fig. 2.—Acute nephritis, Case 2. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On March 8 the patient received three doses of 0.1 gm. each of theocin.

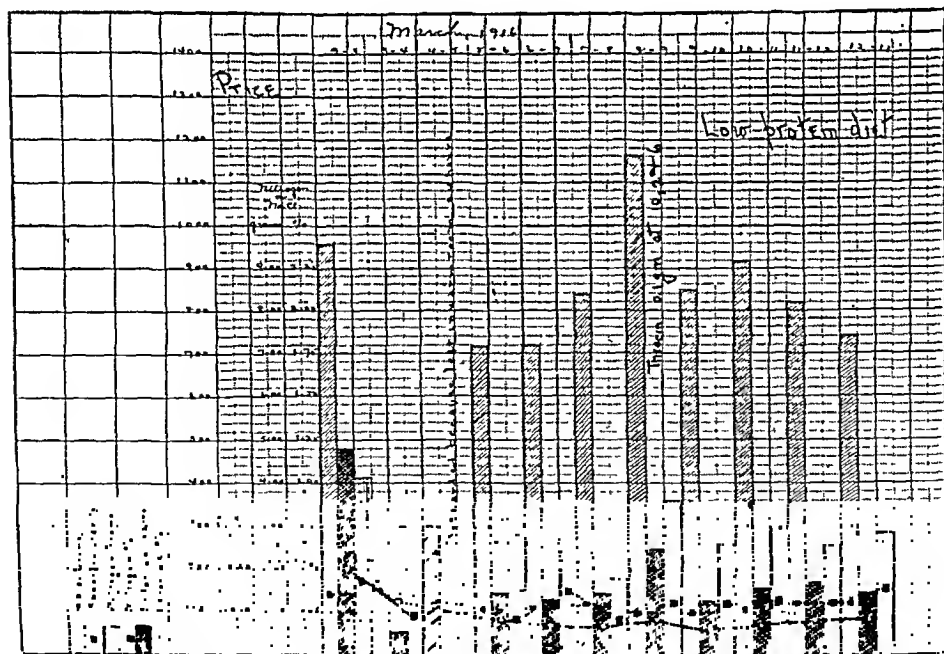


Fig. 3.—Acute nephritis, Case 3. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On March 8 the patient received three doses of 0.1 gm. each of theocin.

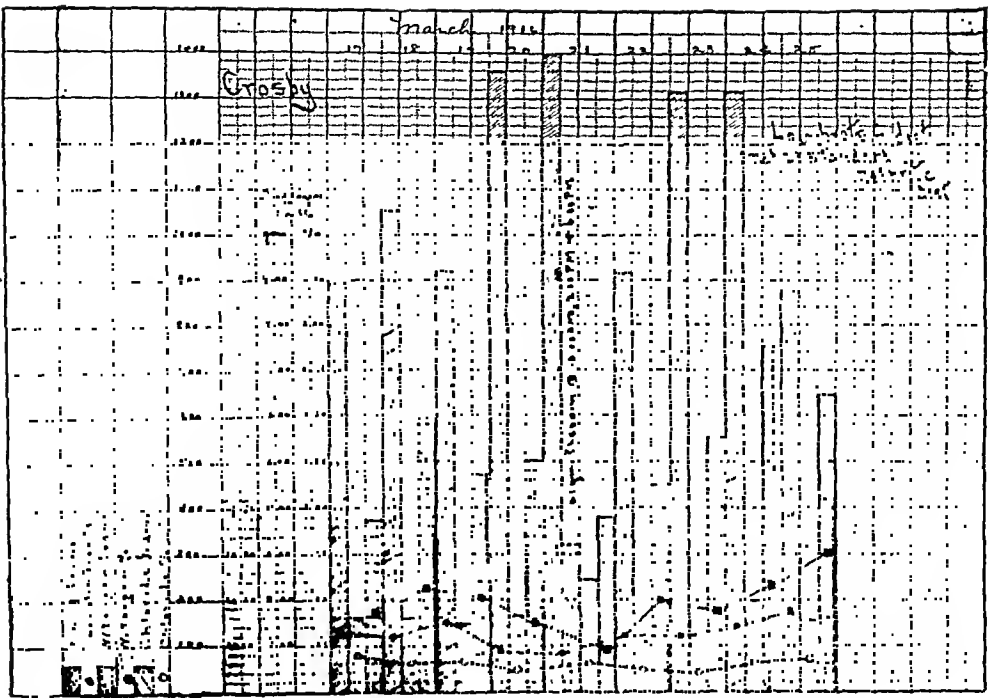


Fig. 4.—Acute nephritis, Case 4. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On March 21 the patient received three doses of 0.1 gm. each of theocin.

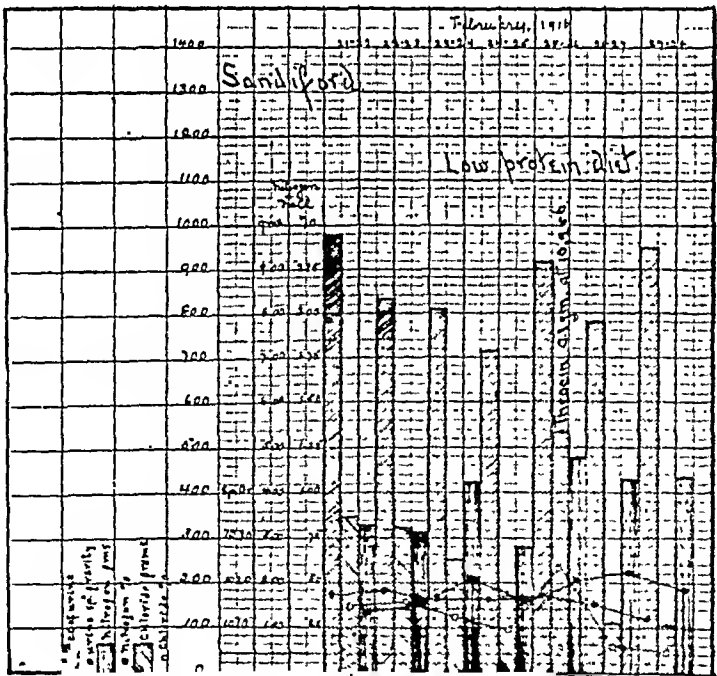
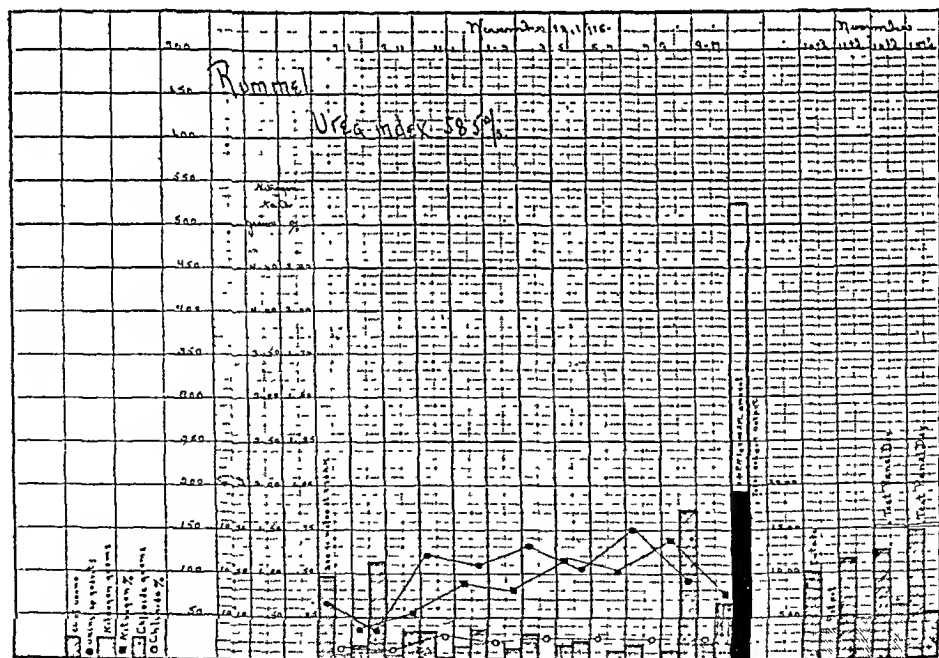
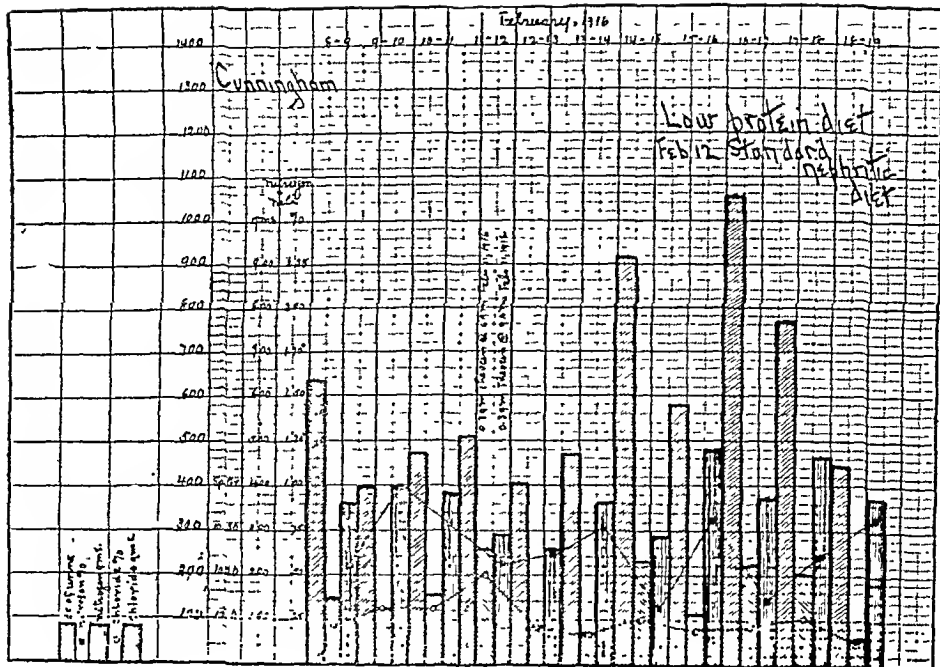


Fig. 5.—Chronic nephritis, Case 1.—The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On February 25 the patient received three doses of 0.1 gm. each of theocin.



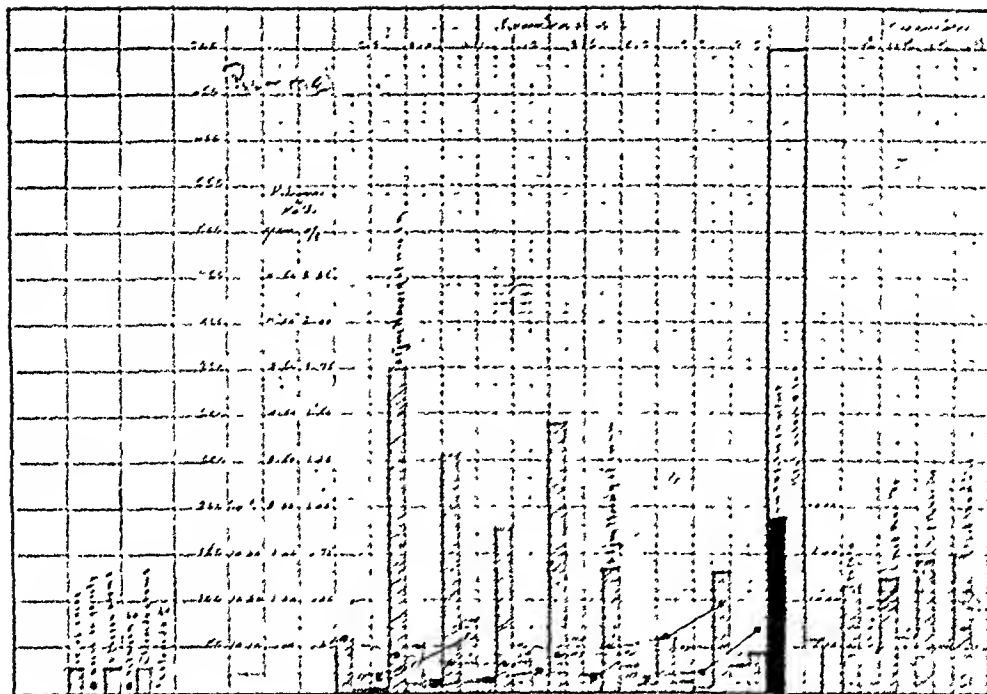


Fig. 8.—Same case as shown in Figure 7, test of November 14. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid line joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

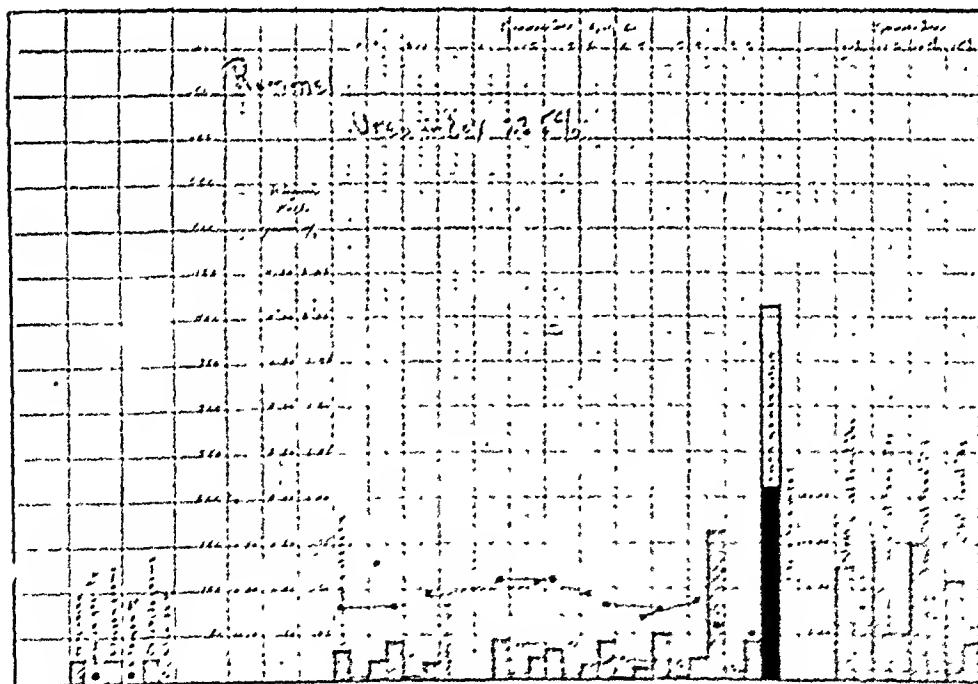


Fig. 9.—Same case as shown in Figure 7 and 8, test of November 15. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid line joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

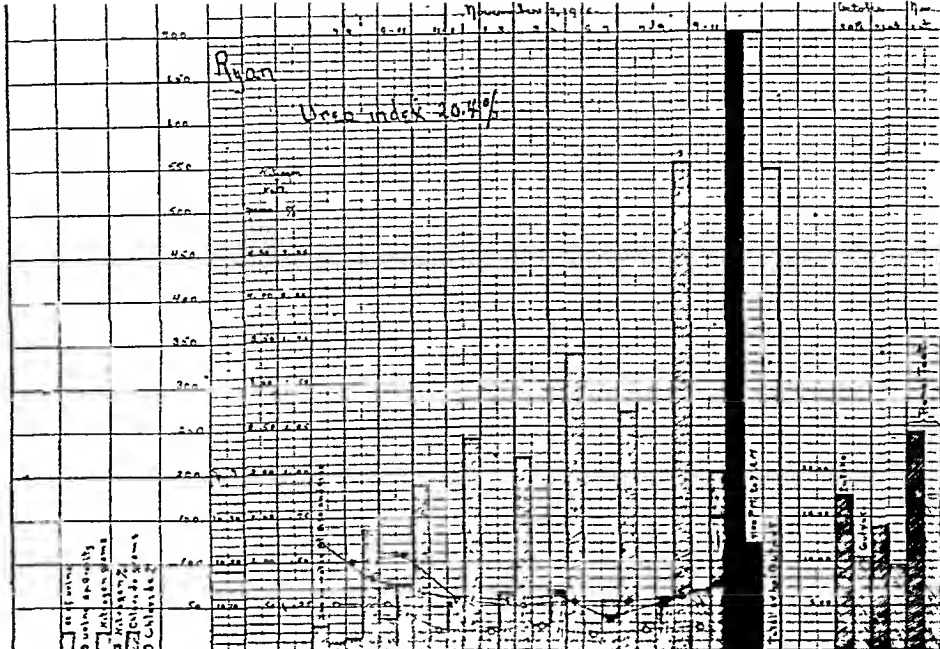


Fig. 10.—Chronic nephritis, Case 5, test on November 2. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

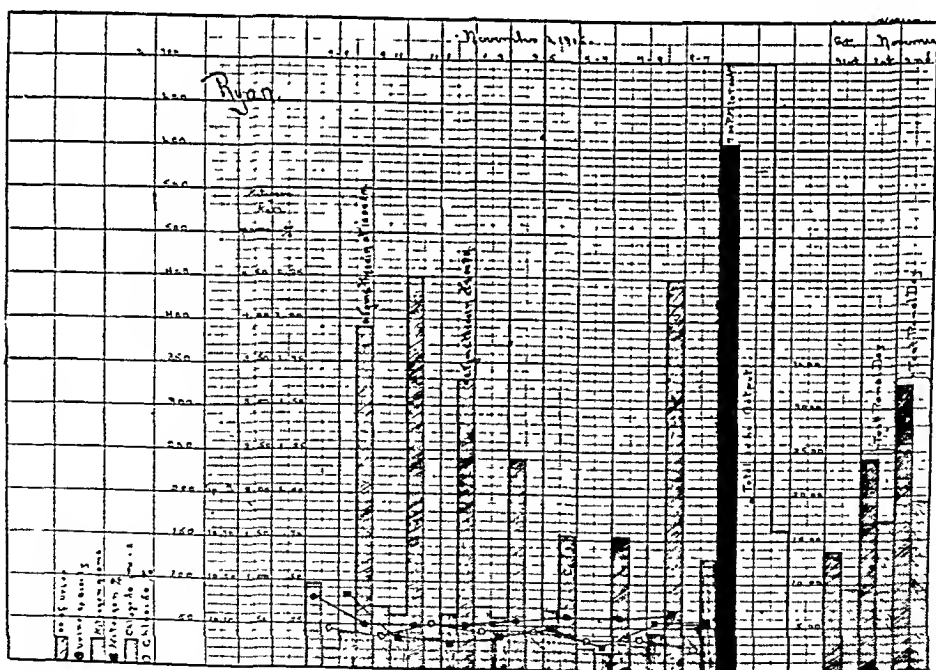


Fig. 11.—Same case as shown in Figure 10, test on November 3. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

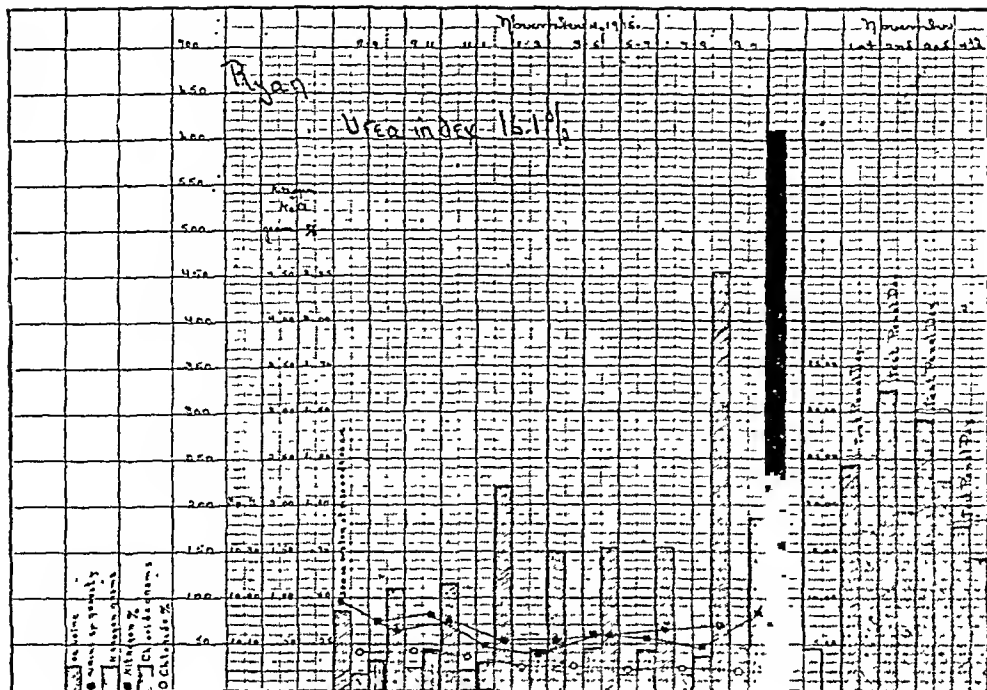


Fig. 12.—Same case as shown in Figures 10 and 11, test on November 4. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and the urine output in the days preceding the test day.

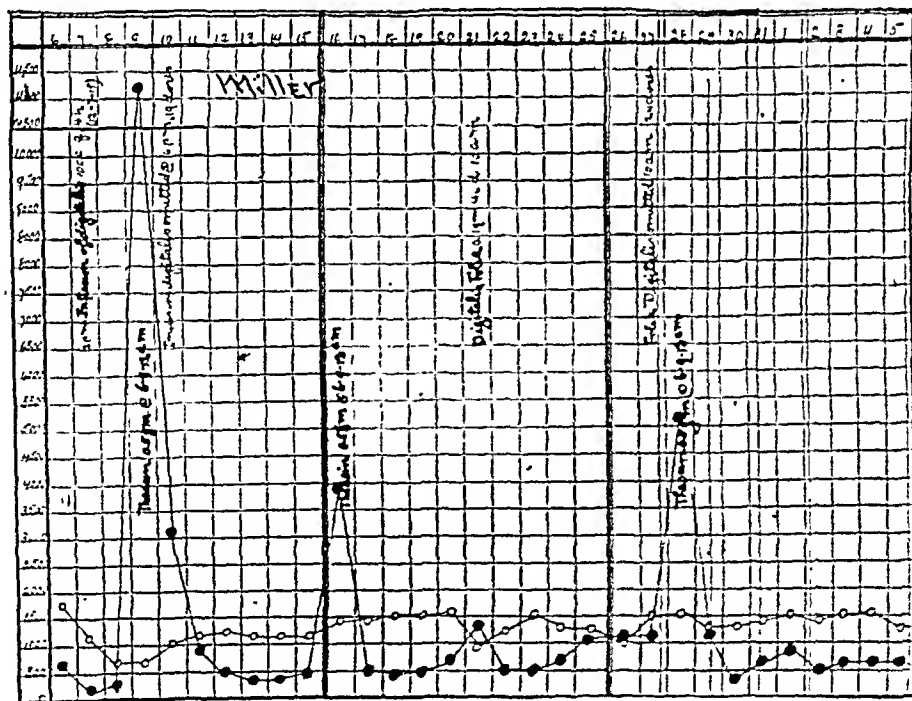


Fig. 13.—Cardiorenal disease, Case 1. The black dots and connecting lines indicate the amount of urine in cubic centimeters. The circles connected by lines indicate the fluid intake of the patient in cubic centimeters.

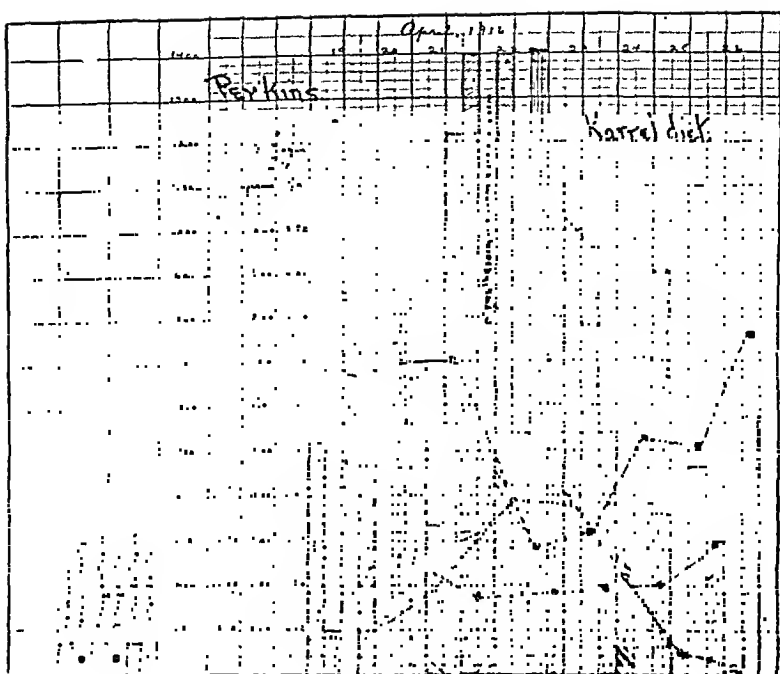


Fig. 14.—Cardiorenal disease, Case 2. The series of columns give the amount of urine, sodium chlorid and nitrogen in each twenty-four hour portion of urine. The lines joining dots in the first column of each series of three columns gives the specific gravity of the urine. The lines joining circles in the second column of each series of three columns gives the percentage concentration of sodium chlorid. The lines joining squares in the third column of each series of three columns gives the percentage concentration of nitrogen. On April 22 the patient received three doses of 0.2 gm. each of theocin.

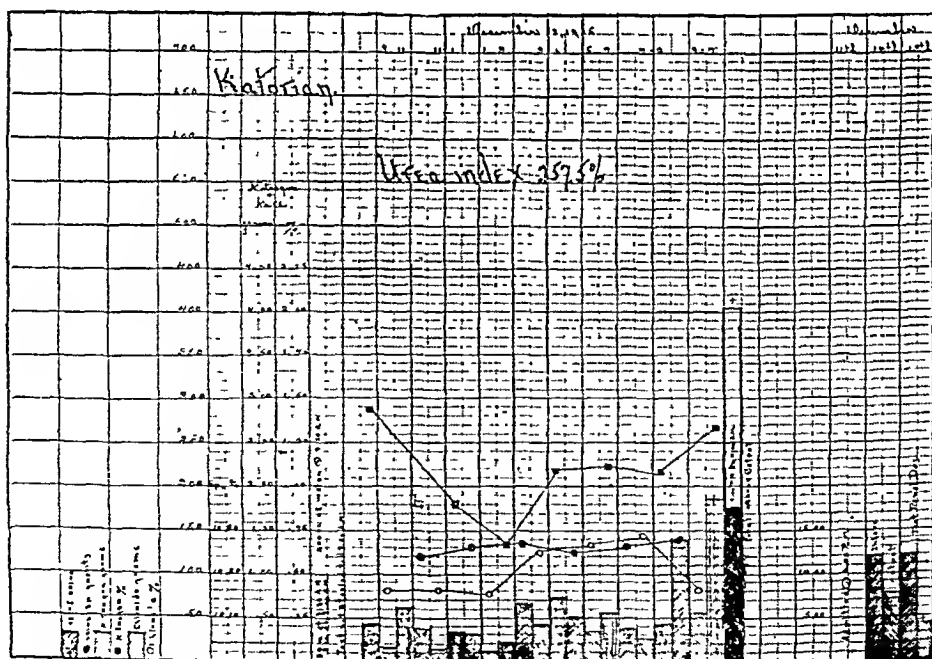


Fig. 15.—Cardiorenal disease, Case 4, test on December 13. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

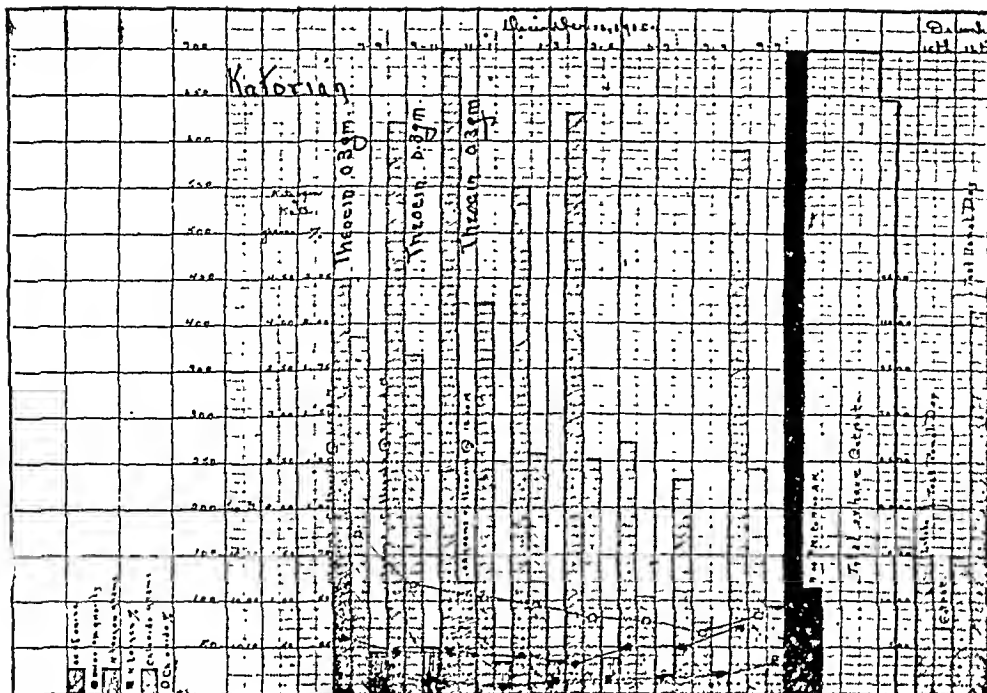


Fig. 16.—Same case as shown in Figure 15, test on December 16. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

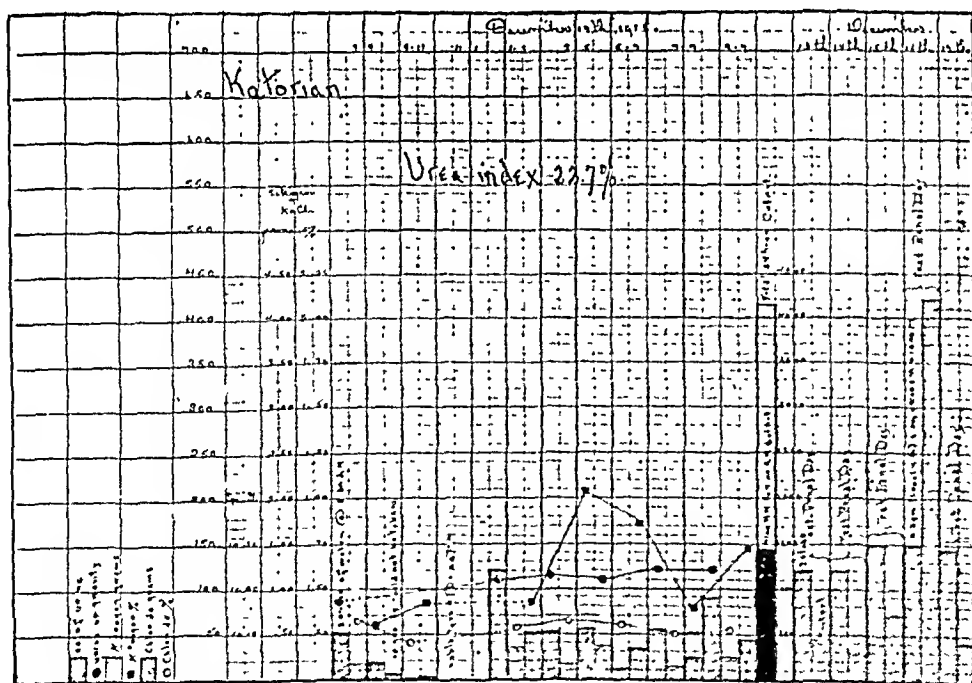


Fig. 17.—Same case as shown in Figures 15 and 16, test on December 17. The series of columns beginning at the left give the amount of urine, sodium chlorid and nitrogen in each two-hour portion from 7 a. m. to 9 p. m., and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

THE TOXIC EFFECTS OF UREA ON NORMAL INDIVIDUALS*

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In order to throw light on the nature of uremia, many investigators have studied the physiologic effects produced when urea is administered to or injected into animals. The majority of those who have undertaken such studies were unable to demonstrate that urea acted as a poison. Only a few have succeeded in producing definite toxic effects. For example, Herter and Wakeman,¹ as well as Marshall and Davis,² found that approximately 1 per cent. of the body weight must be injected into animals in order to produce a fatal result. Ascoli,³ in reviewing the earlier literature, has sought to explain the occasional toxic effects observed on one or more of the following assumptions: (1) the urea used was not pure, (2) it was injected intravenously in too concentrated a solution, or (3) where used in dilute solution the effects were attributable to the excessive amounts of liquid rapidly introduced into the body. Under any circumstances it is clear that in animal experiments definite toxic effects can be produced only when extraordinarily large doses of the drug were given, doses which presumably raise the concentration of urea in the body above that which is encountered in most cases of uremia in man. For these reasons the view has become generally accepted that the toxic effects of urea in any concentration encountered in patients are negligible and that the symptoms of uremia are due to the action of the other and more poisonous substances.

Recent advances in our knowledge concerning the toxic symptoms presented by patients in the more advanced stages of nephritis permit one, however, to approach this question from a new point of view. It seems established that uremia, in the sense of any toxic state com-

* Submitted for publication June 12, 1916.

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1. Herter, C. A., and Wakeman, A. J.: On Alterations in the Composition of the Blood Resulting from Double Nephrectomy, *Jour. Exper. Med.*, 1899, iv, 117.

2. Marshall, E. K., Jr., and Davis, D. M.: Urea: Its Distribution in and Elimination from the Body, *Jour. Biol. Chem.*, 1914, xviii, 53.

3. Ascoli, G.: *Vorlesungen über Urämie*, Jena, 1903, p. 130.

plicating renal disease, includes a variety of distinct conditions. In certain patients, toxic symptoms occur when the urea and the total incoagulable nitrogen of the blood are either not increased or are increased to such a small extent that the symptoms observed can hardly be attributed either to the urea or to an increase in the total incoagulable nitrogen of the blood. This appears to be particularly true of those cases of uremia in which generalized epileptiform convulsions dominate the symptomatology. In such cases particularly, the search for a specific toxic substance seems indicated, and N. B. Foster⁴ has reported the isolation of a toxic base from the blood of patients suffering from the convulsive form of uremia.

On the other hand, it has been shown that during the later stages of nephritis there is not infrequently an increase of urea and of other nitrogenous substances, such as uric acid, creatin, creatinin, and indican in the blood and that when this increase becomes very marked toxic symptoms are present. In such patients the urea not only shows the greatest absolute increase, but its increase is relatively greater than the increase in the sum total of the other nonprotein nitrogenous bodies. Clinical studies have demonstrated furthermore that such patients frequently do not present certain of the classic uremic symptoms. Generalized convulsions, paralyses and prolonged comas are often absent. The symptoms which characterize the advanced stages of nitrogenous retention have been for some years the subject of study, particularly by French clinicians. According to Widál,⁵ for example, the symptoms consist of loss of appetite, fatigue, prostration, mental dulness, somnolence and eventually coma. Reiss,⁶ who has recently described this condition as the asthenic type of uremia, believes that it is characterized clinically by drowsiness and indifference, by bodily fatigue and prostration, and by sudden cardiac death without prolonged coma.

The modern blood studies on nephritic patients have also served to define the relation that exists between the clinical symptoms and the level of urea and nonprotein nitrogen in the blood. While it is difficult, by reason of individual variations, to fix accurately the level at which the accumulation of nitrogenous waste products leads to the production of symptoms, nevertheless one may say in general that symptoms characteristic of asthenic uremia are rarely well defined when the concentration of urea in the blood is less than 100 mg. per

4. Foster, N. B.: The Isolation of a Toxic Substance from the Blood of Uremic Patients, *Tr. Assn. Am. Phys.*, 1915, xxx, 305.

5. Widál, F., and Lemierre, A.: Die diätetische Behandlung der Nierenentzündungen, *Ergebn. d. inn. Med. u. Kinderh.*, 1909, iv, 523.

6. Reiss, E.: Zur Klinik und Einteilung der Urämie, *Ztschr. f. klin. Med.*, 1914, lxxx, 97, 424, 452.

TABLE 1 (EXPERIMENT 1, A. W. H., DEC. 23, 1915).—EFFECT OF INGESTION OF 100 GM. UREA IN ONE DOSE

Time	Urea Taken, Gm.	Urine Passed, O.c.	Rate of Diuresis, 24 Hr., O.c.	Urea per 100 O.c. Urine, Gm.	Urea Excreted, Gm.	Rate of Urea Excretion 24 Hr., Gm.	Urea in Blood, Gm. per 100 O.c.	Ambard	IIb., per Cent.	Remarks
9:26 to 10:02 a. m.	...	21.8	870	3.02	0.66	26.3	0.010	0.071	93	Considerable nausea
10:05 to 10:18	100									
10:02 to 10:37	...	77.7	3,200	2.37	1.81	75.8	(0.072)*			
10:37 to 11:09	...	230	10,350	2.44	5.61	252.51	0.147	0.093	87	11:00, slight headache, stupor, sleepy, nausea less
11:09 to 11:29	...	134	9,650	2.5	3.35	211.25	(0.166)	11:12, headache, dizzy; 11:15, headache worse; blood pressure, 120 and 85
11:29 to 12:02	...	240	10,170	2.66	6.38	278.5	0.2	0.118	77	11:30, headache, dizzy; 11:36, soft stool, weak, dizzy; 11:57, headache
12:02 to 12:30	...	158	8,130	2.50	4.01	208	(0.167)	12:30, diarrheal stool; better but still headache
12:30 to 1:00 p. m.	...	192	9,220	2.90	5.68	272.9	(0.193)	1:00, headache and weak
1:00 to 1:30	...	127	6,100	3.35	4.24	201	(0.168)	
1:30 to 2:07	...	161	6,270	3.77	6.07	236.4	0.10	0.107	72	Feel fairly comfortable, but unable to work
2:07 to 3:10	...	267	6,100	3.52	9.4	215	(0.167)	Unable to do customary work during the late afternoon

* The amount of urea in the blood when enclosed in parentheses in this and the following tables was estimated by the method described in the text.

100 c.c. of blood and that they are rarely absent when the concentration exceeds 200 mg. From clinical observations, therefore, one would be inclined to place the point at which the accumulation of urea might possibly cause symptoms between the two limits of 100 and 200 mg. of urea per 100 c.c. of blood.

The bodily and mental prostration which characterizes the earlier stages of asthenic uremia may readily escape detection in animal experiments. For this reason it seemed a matter of some importance to study once again the toxic effects of this compound, using men as the subjects of the study. Our experiments were therefore undertaken with the view of ascertaining whether normal persons manifest toxic symptoms when sufficient urea has been taken by mouth to raise the urea in the blood to the levels encountered in asthenic uremia. Since urea diffuses rapidly from the blood into the tissues, it is evident that in order to attain such concentrations in the blood large quantities of urea must be given. Furthermore, since urea is rapidly eliminated from the body by way of the urine, it is evident that the large quantity of urea must be taken within a brief period of time and that prolonged experiments can be carried out only with considerable difficulty. As will appear in the following experiments, the ingestion of 100 gm. of urea within a few hours raises the level of blood urea in a normal individual to from 150 to 245 mg. per 100 c.c. Such concentrations are comparable with those encountered in the asthenic type of uremia and if the symptoms in the latter condition are in any way dependent on the concentration of urea in the blood and tissues, symptoms should occur under the conditions of our experiment.

Outline of Experiments: Five experiments were performed, four on the authors themselves and one on Dr. F. N. Wilson, who volunteered for this purpose. The subject of the experiment presented himself to the clinical laboratory after his usual breakfast and emptied his bladder. The urea content of his blood was determined and this was compared with the output of urea in the urine by the method of Ambard.⁷ The subject then took the urea dissolved in water, either in a single dose or in doses divided over a period of from three to six hours. In three instances the intake was completed before the noon meal, while in two others one or more doses were taken after the meal. The successive specimens of urine were collected, measured and analyzed for urea, over a period varying from nine to thirty hours after the beginning of the experiment. The concentration of urea in the blood and the Ambard coefficient were determined on two or more occasions during the afternoon of the experimental day and

7. Ambard, L., and Weill, A.: Les lois numeriques de la sécrétion rénale de l'urée et du chlorure de sodium, *Jour. physiol. et pathol. génér.*, 1912, xiv, 753.

TABLE 3 (EXPERIMENT 3, Q. O. G., DEC. 27, 1915).—EFFECT OF INGESTION OF 100 GM. UREA IN THREE HOURS

Time	Urea Taken, Gm.	Urine Passed, C.c.	Rate of Diuresis, 24 Hr., C.c.	Urea per 100 C.c. Urine, Gm.	Urea Excreted, Gm.	Rate of Urea Excretion 24 Hr., Gm.	Urea in Blood, Gm. per 100 C.c.	Ambard	Hb., per Cent.	Remarks
10:20 to 10:55 a. m.	...	22	1,220	2.51	0.23	22.1	0.042	0.575	85	Weight 177 pounds
11:00	25	11:23, slight nausea, slight headache and dizzy; 11:45, better
10:55 to 12:25	...	231	2,700	3.01	7.92	112.5	(0.565)	
12:00 m.	25	250	5,170	3.52	9.82	122.7	(0.153)	12:37, some headache, sleepy, dizziness; somewhat unsteady when attempting to walk or work with hands
12:25 to 1:44 p. m.	...	154	7,150	4.02	6.17	237.4	(0.222)	1:20, no nausea, more headache, dull, somnolent; 1:40, dull headache, some throbbing in ears and head, stupid
2:00	25	123	7,720	4.65	7.3	212.9	0.245	0.122	99	2:15, headache worse, no nausea, dizziness about the same
2:15 to 2:51	...	221	6,450	4.24	9.59	231.5	(0.231)	2:54, no nausea, dull frontal headache, difficult to concentrate attention, sleepy
3:40 to 4:25	...	261	6,710	4.69	10.44	293.4	(0.218)	3:40, headache no worse, but more stupid and sleepy; difficult to do any work
4:25 to 5:22	...	193	5,520	4.39	9.27	220.5	(0.226)	5:10, dull headache; restless and irritable; weight 170 pounds
5:22 to 6:04	...	154	5,220	4.93	6.2	212.3	0.187	0.115	81	5:20, headache began to go away, but still an effort to concentrate and to do any work
6:04 to 7:43	...	223	2,230	5.22	12.65	175.4	(0.181)	6:20, excessively irritable, but mental processes are slow
7:43 to 10:50	...	245	2,150	4.75	14.75	143.4	(0.152)	8:00, feeling better
10:50 to 2:25 a. m.	...	245	2,210	4.12	11.25	91.2	(0.114)	
2:25 to 4:25	...	237	1,140	5.64	16.2	66.6	(0.660)	
4:25 to 10:43	...	73	844	6.43	5.91	72.4	(0.635)	
10:43 to 11:22	...	12.5	653	6.12	1.12	11.3	0.674	0.022	94	
11:22 to 2:45 p. m.	...	171	717	4.51	6.25	34.7	(0.662)	

once on the following morning. No restriction was placed on the exercise taken, the amount of water drunk or the amount or kind of food eaten.

The quantity of urea in the blood and urine was determined by Van Slyke's urease method. In the earlier experiments the final titrations were performed, using alizarin monosulphate as an indicator. At the suggestion of H. H. Willard, however, methyl red was used as an indicator in one experiment (Experiment 2) and was found to give a more definite end reading. The hemoglobin in each specimen of blood drawn was determined by the Autenriech colorimeter. The results of our observations are shown in Tables 1 to 5.

EFFECT ON UREA CONTENT OF THE BLOOD AND URINE

During these observations the amount of urea taken varied from 100 to 125 gm. In the first experiment 100 were taken within fifteen minutes, in the second 125 gm. were taken in 25 gm. doses at hourly intervals, in the third and fourth 100 gm. were taken in a similar manner, while in the fifth experiment 110 gm. were taken during six hours, the major portion being taken during the first three hours.

The effect of the ingestion was apparent in the first specimen of urine subsequently passed. This showed a more rapid diuresis and an increased excretion of urea. The rate of excretion rapidly augmented and reached a maximum within a few hours after the last dose had been taken. It was evident, therefore, that absorption from the gastro-intestinal canal was very rapid. At the height of the experiment the maximum rate of elimination of urea varied in the different experiments from 11 to 14.8 gm. of urea per hour. From this maximum the rate of elimination fell, at first rapidly and then more slowly. At the end of twenty-four hours it had approached but not reached the original rate. The amount of urea excreted within the twenty-four hours was greater than the amount ingested, but in view of the fact that the urea level in the blood had not yet returned completely to the normal at this time, it is fair to assume that the amount excreted in the twenty-four hours was somewhat less than the sum of what had been ingested and what had been formed in the body during this time.

The amount of urea in the blood as determined by direct analysis also reached a maximum within a few hours after the last dose had been taken. This maximum varied from 150 to 245 mg. per 100 c.c. of blood, indicating that we had attained our object of increasing the concentration of urea in the blood to amounts that were comparable with those encountered in the asthenic type of uremia.

According to Ambard, there exists, for any person, a constant

TABLE 4 (EXPERIMENT 4, A. D. W., JAN. 3, 1916).—EFFECT OF INGESTION OF 100 GM. UREA IN THREE HOURS

Time	Urea Taken, Gm.	Urine Passed, C.c.	Rate of Diuresis, 24 Hr., C.c.	Urea per 100 C.c. Urine, Gm.	Urea Excreted, Gm.	Rate of Urea Excretion 24 Hr., Gm.	Urea in Blood, Gm. per 100 C.c.	Ambard	Hb., per Cent.	Remarks
8:30 to 9:08 a. m.	...	90	3,420	1.2	1.08	41	0.04	0.075	93	Weight 141¾ pounds
9:15	25	9:15, nausea, passing off in a few minutes
9:08 to 9:14	...	471	18,900	1.2	5.7	227.5	(0.103)	
10:15	25	
9:14 to 10:56	...	384	7,680	2.5	9.6	192.2	(0.128)	10:40, feels uneasy; slight headache passing off in a few minutes
11:15	25	
10:56 to 12:08 p. m.	...	323	6,460	2.91	9.4	187.9	(0.119)	11:25, rather dopy, head not clear; blood pressure 130 and 94; no nausea
12:15	25	
12:08 to 12:27	...	91	6,800	3.24	2.9	223.2	(0.18)	12:15, headache and dizziness; sleepy
12:27 to 1:03	...	171	6,810	3.37	5.7	230.7	0.193	0.118	87	12:45, feels better now; 12:50, lunch; appetite good; nervous; hands unsteady
1:03 to 2:15	...	391	7,850	3.84	15	300.3	(0.223)	1:25, dizzy; hands and feet unsteady; head feels heavy
2:15 to 3:27	...	359	7,150	3.6	12.9	258.5	(0.203)	2:15, dizzy and unsteady; 3:00, tired physically and mentally; effort required to accomplish anything; 3:15, blood pressure 130 and 86
3:27 to 4:39	...	333	6,600	3.24	10.8	215.8	(0.177)	4:15, head still aches; intellect cloudy; thinks slowly; dizziness less marked; feet heavy and drag
4:39 to 5:15	...	314	12,560	2.04	6.4	256.3	0.17	0.112	75	
5:15 to 5:51	...	222	8,880	2.16	1.8	191.8	(0.150)	5:10, weight 112¾ pounds
5:51 to 6:35	...	270	8,810	1.88	5.1	166.4	(0.132)	
6:35 to 11:00	...	920	5,000	2.66	24.4	133	(0.125)	
11:00 to 3:00 a. m.	...	556	1,480	4.56	24.2	64.5	(0.064)	
8:00 to 10:05	...	133	1,620	4.36	5.8	66.7	(0.09)	
10:05 to 11:00	...	235	5,200	1.51	3.5	79.9	(0.070)	
11:00 to 11:15	...	161	6,410	0.98	1.53	63.4	0.659	0.094	86	..6:15, headache and tired

TABLE 5 (EXPERIMENT 5, F. N. W.).—EFFECT OF INGESTION OF 110 GM. UREA IN SIX HOURS

Time	Urea Taken, Gm.	Urine Passed, O.e.	Ratio of Diuretics, 24 Hr., O.e.	Urea per 100 O.e. Urine, Gm.	Urea Excreted, Gm.	Ratio of Urea Excretion, 24 Hr., Gm.	Urea in Blood, Gm. per 100 O.e.	Ambard	Hb., per Cent.	Remarks
8:12 to 9:18 a. m.	...	35.5	1,420	2.66	0.0	37.8	0.036	0.053	95	
9:30	25									
9:18 to 10:30	...	183	3,060	2.74	5.1	100.3	(0.063)	9:30, feels well; 9:40, head a little thick
10:25	25									
10:30 to 11:10	...	173	5,410	4.13	7.1	223.5	(0.111)	11:45, head a little thick; otherwise well
11:30	20									
11:10 to 12:10 p. m.	...	230	5,520	4.12	10.1	213.9	(0.122)			
12:30	10									
12:10 to 1:00	...	197	6,450	5.52	10.9	355.9	(0.103)	12:35, little weak and thick headed; weak and slightly drowsy; 12:52, less sleepy
1:30	10									
1:00 to 1:18	...	181	5,130	4.33	7.8	235.1	(0.129)	1:18, feels well
2:30	10									
1:18 to 2:10	...	218	5,860	4.03	10	236.1	(0.133)			
2:10 to 3:29	...	181	6,510	4.18	7.6	272.1	0.150	0.079	85	3:25, slight headache
3:30	10									
3:29 to 4:10	..	227	6,180	3.89	7.7	252.1	(0.138)	4:02, headache
4:10 to 4:50	...	179	6,410	4.14	7.1	206.0	(0.141)			
4:50 to 6:33	...	307	5,620	3.67	13.3	205.3	0.117			
6:33 to 8:28	...	422	5,380	3.89	16.1	209.5	(0.111)	Headache increased until 8:30, at which time it was quite severe; went to sleep and headache passed off during night
8:26 to 9:30 a. m.	...	681	1,610	5.83	30.9	95.0	(0.091)			
9:30 to 9:40	...	132	1,120	5.32	7	59.6	(0.041)			
9:20 to 9:45	...	23	1,320	5.57	1.3	73.5	(0.015)			
9:45 to 10:21	...	31	1,300	4.51	1.5	61.7	0.039	0.012	95	

relation between the concentration of urea in the blood and its excretion in the urine. Ambard's formula is as follows:

$$k = \frac{U}{\sqrt{D} \sqrt{\frac{C}{25}}}$$

in which U represents the number of grams of urea in 1,000 c.c. of blood, D the output of urea over the observed period calculated for twenty-four hours, and C the concentration of urea in the urine excreted, expressed in grams per liter. In the above experiments the Ambard factor k was determined for each specimen of blood drawn. It was found to vary far less than any of the other data that enter into it, that is, the concentration of urea in the blood, the rate of excretion of urea and the diuresis. Nevertheless, the factor did not remain constant in any of the experiments, but regularly showed a rise when the urea concentration in the blood rose and a fall when the urea concentration in the blood fell. One might be inclined to interpret the rise of the Ambard factor during our experiments as an indication of renal fatigue, owing to the extraordinary strain placed on the kidney in the way of excreting urea. Against this interpretation, however, is the fact that the Ambard factor regularly fell during the afternoon of the experiment, although one would expect that here if anywhere the kidney would show signs of fatigue, owing to the continued excessive work. It seems to us probable therefore that the Ambard "constant" is but an approximation to the actual facts and that the kidney does not work with the mathematical precision that might be assumed from such a formula.

Nevertheless, we found the Ambard formula of considerable service in that by this means we were able to estimate the approximate concentration of urea in the blood at numerous points of our experiment. These estimations were made as follows. The determined points on the Ambard curve were connected by straight lines and the Ambard factor was assumed to correspond to the point at which these connecting lines crossed the time intervals. Having this assumed constant and knowing the rate of diuresis and the rate of urea elimination in the urine, we were able to estimate the approximate level of urea in the blood according to the following transposition of the Ambard formula:

$$U = k \sqrt{D} \sqrt{\frac{C}{25}}$$

in which the letters have the same significance as in the original formula. In this way the approximate level of blood urea could be interpolated at numerous points during an experiment. In the tables

these interpolations have been enclosed in parentheses. The advantage of such interpolations is at once obvious when one endeavors to compare the onset and duration of symptoms with the concentration of urea in the blood at different times during an experiment.

EFFECT ON WATER METABOLISM

No restriction of fluid intake was carried out in these experiments and with one exception (Experiment 3) the fluid intake was not recorded. Although it was not possible to follow accurately the water metabolism in the body, nevertheless our observations indicate that the ingestion of such large quantities of urea is not without an effect on the fluids of the body. Considerable thirst was experienced during and for a time after the ingestion of the urea, and as the subjects were allowed to drink freely, considerable water was taken to satisfy this thirst. At the same time a marked diuresis accompanied the elimination of the large quantities of urea. The body weight varied according to the balance between the intake and the output of fluid. In Experiment 4 the subject drank very large quantities of water and gained $\frac{1}{2}$ pound during the day and lost $1\frac{1}{2}$ pounds during the following night. In Experiment 3 the subject lost 7 pounds between the onset of the experiment and 5 o'clock in the afternoon. In Experiment 2, 4 pounds were lost in twenty-four hours and the original weight was not recovered for about four days. The changes in body weight were not recorded in Experiments 1 and 5.

TABLE 6.—EFFECT ON THE HEMOGLOBIN

Experiment	Hemoglobin Before, per Cent.	Hemoglobin After, per Cent.	
		Same Day	Next Morning
1	93	87, 77, 72	92
2	(93)	83, 85	
3	95	90, 81	94
4	93	87, 75	86
5	95	85	95

During each experiment there occurred a definite fall in the hemoglobin, as is shown in Table 6. This fall was usually most pronounced late in the afternoon of the experimental day, when the concentration of urea in the blood had already begun to fall. On the following morning the hemoglobin had returned more or less completely to the normal. Such a transient reduction in the hemoglobin indicates a dilution of the blood and since it also occurred even when the subject was rapidly losing weight (Experiment 3), the necessary liquids in such a case must have been withdrawn from the tissues. This dilution

of the blood during the diuresis following these excessive quantities of urea is perhaps comparable to that which may occur after the ingestion of sodium chlorid or the saline diuretics. It probably played some part in provoking the diuresis in our experiments.

THE SYMPTOMS

Each subject noted his symptoms as they occurred. By comparing these notes with the concentration of urea in the blood at the time, it was possible to add to the objective character of the experiments and to determine to what extent the symptoms corresponded with an augmented concentration of urea in the blood. Experiment 5 differed from the first four, partly because the urea concentration did not reach the same high level and partly because the symptoms were less marked and not so definitely related to the maximum concentration of urea in the blood. For this reason it will be considered separately.

In all of the first four experiments some nausea was experienced after taking the first dose of urea, but vomiting did not occur. The nausea was most marked in Experiment 1, in which 100 gm. of urea were taken within fifteen minutes. In Experiment 2 it was present after the first three doses and was absent after the last two. In Experiments 3 and 4 slight nausea was experienced after the first dose, but none after the next three. In all cases the nausea had disappeared before the concentration in the blood had reached its maximum. It is evident therefore that in these experiments the nausea did not depend on a high concentration of urea in the body fluids or tissues, but was probably associated with local changes in the gastrointestinal canal. The subject of Experiments 1 and 2 had diarrheal evacuations of the intestines a few hours after the ingestion of the urea. The other subjects experienced no intestinal disturbances.

In each of the first four experiments definite symptoms occurred at the time that the concentration of urea in the blood was highest. Headache was first noted, the sensation usually being described as a tight feeling in the head or as a dull ache. This headache was soon followed by dizzy sensations, which were in turn followed by apathy, drowsiness and an inability to do the customary amount of work. Feelings of bodily fatigue and weakness occurred in each case. The subjects of Experiments 3 and 4, on whom fell the burden of the chemical determinations, were in each case unable to carry on this work during the afternoon which followed the taking of the urea, by reason of mental and bodily fatigue, together with an inability to concentrate the attention. In both instances the hands were unsteady. The subject of Experiment 3 became excessively irritable during the afternoon, while the subject of Experiment 4 complained particularly of bodily fatigue. In Experiment 2 at the height of the intoxication the subject found some difficulty in pronouncing words distinctly.

These cerebral and bodily symptoms were most pronounced at the time of maximum concentration of urea in the blood. In all cases they appeared in a definite form at about the time that the blood urea reached a concentration of 150 to 160 mg. per 100 c.c. It is noteworthy that they appeared to be less intense at corresponding levels during the afternoon, when the amount of urea in the body was lessening.

The subject of Experiment 5 did not show so high a concentration of blood urea as did the other subjects. This was due in part to the fact that his ingestion of urea extended over a longer period. In part it was due to the fact that he showed an unusually rapid excretion, with an unusually low Ambard coefficient (increased renal permeability to urea). This subject complained at first of feeling somewhat thick headed, and later of being somewhat drowsy and disinclined to work. The latter symptoms coincided with the maximum concentration of urea in his blood (163 mg.). During the afternoon a headache developed, which gradually became more marked as the afternoon advanced and was quite intense at bedtime. During the night it disappeared. This subject suffers from occasional headaches (migraine?) and the experiment seems to have induced a headache of the usual type, but one of unusual severity. This headache was not due directly to the high concentration of urea in the blood, for it reached its maximum after the concentration in the blood had fallen below 114 mg.

In two experiments (1 and 4) the blood pressures were taken at the height of the intoxication, but in neither case was any marked hypertension present.

The symptoms observed at the maximum concentration of urea in the blood during our experiments correspond almost exactly with those described by Reiss for the asthenic type of uremia, that is, drowsiness and indifference, bodily fatigue and prostration. The loss of appetite described by Widal did not occur. On the other hand, headache and dizziness were quite constant. The symptoms observed developed at approximately the same level of blood urea in all subjects and this level corresponded roughly to that which is associated with definite and unmistakable symptoms in asthenic uremia.

To the analogy that has been drawn between the symptoms observed in these experiments and those of asthenic uremia, the objection might be raised that the symptoms observed after ingestion were due to the rapid entrance of urea into the tissues and that had the high level been maintained for some time the symptoms would have disappeared. This criticism is supported by the fact that the symptoms were usually more marked at a given level of blood urea when the urea was accumulating in the body than they were at the same level

of blood urea when the urea in the body was lessening. It seems probable, therefore, that a portion of the symptoms observed may have been due to the acute character of the experiment. Nevertheless, the following facts indicate that the high level of urea in the body was responsible for the major portion of the symptoms. First, no definite symptoms occurred while the blood urea was rising from 40 to 150 mg. per 100 c.c., nor have symptoms been observed by other observers when from 20 to 30 gm. of urea have been given in a single dose. Second, the onset of symptoms occurred in each of our subjects when the level of blood urea had passed a definite point (about 150 mg.). Third, the symptoms, though less marked, persisted until the blood urea had fallen to approximately 160 mg. per 100 c.c. For these reasons we believe that the symptoms in our experiments were due, in the main, not to the sudden entrance of urea into the tissues, but to its high concentration therein.

It seems probable, therefore, that when as a result of nephritis the blood urea exceeds a concentration of 150 mg. per 100 c.c., the symptoms of bodily and mental asthenia may be explained in part as being due to the high concentration of urea in the body fluids and tissues. This by no means excludes the possibility that other substances may play a rôle in producing the symptoms of this type of uremia and indeed the fact that animals die only when extraordinary doses of urea are administered suggests that the fatal outcome of asthenic uremia in man may be due to other substances than urea.

DISTRIBUTION OF UREA TO THE TISSUES

It is well known that urea diffuses readily between the blood and the tissues. This fact is also apparent in our experiments. Assuming, for example, that there are 5 liters of blood in the body and that all of the urea administered remained in the blood, it would require but 10 gm. of urea to give a concentration of 200 mg. per 100 c.c. of blood. Since approximately 100 gm. of urea were required to raise the blood urea to this level, it is evident that the major portion of the urea absorbed from the gastro-intestinal canal must have passed rapidly from the blood into the tissues.

One may estimate roughly the additional amount of urea in the body at any time during our experiments, for this will equal the amount absorbed from the intestinal canal plus that formed by metabolism in the body and minus that eliminated through the excreta. For purposes of calculation we have assumed (1) that the urea was completely absorbed from the intestinal canal, (2) that it was eliminated entirely by way of the urine and (3) that the rate of metabolism was such that 1.5 gm. of urea were formed hourly in the body. If these assumptions are made, then the total amount of urea in the body

at any time during the experiment may be estimated. Such estimations are shown in Table 7.

The various possible errors in the assumptions on which these calculations are based do not permit one to draw any definite conclusion as to the exact relation that exists between the amount of urea in the body and its concentration in the blood. It should be noted, however, that in the first two experiments diarrheal discharges occurred and that in this way a certain amount of urea was probably lost from the body. If this were the case, the estimated amount of urea in the body would have been less and the relation (*c*) would have been greater. Similarly, in Experiment 5 and in the first estimation of Experiment 4 the blood was drawn about half an hour after the last dose of urea had been given. If one were to assume that this had not been entirely absorbed the excess in the body would again be less and the relation (*c*) greater. It would appear, therefore, that for every gram of excess urea in the body the concentration of urea in the blood rose at least 2.5 mg. per 100 c.c. of blood.

TABLE 7.—EXCESS UREA IN THE BODY AND ITS RELATION TO THE EXCESS IN THE BLOOD

Experiment	Body Weight, Kg.	Time Since First Determination, Hours	Excess Urea in Body, Gm. (<i>a</i>)	Excess in Blood, Mg. (<i>b</i>)	Relation <i>b</i> to <i>a</i> (<i>c</i>)
1	75	2	89	160	1.8
		4	72	120	1.7
2	75	5	98	178	1.8
		7½	77	156	2.0
3	80	4	79	202	2.8
		7	47	144	3.1
4	65	4	76	153	2.0
		8	36	130	3.6
5	78	6	54	113	2.1

If 1 gm. of urea be uniformly distributed in a body weighing 70 kg. it would cause an increase of concentration amounting to 1.4 mg. per 100 gm. It is evident, therefore, that while the major portion of the urea ingested entered the tissues, its concentration in the body as a whole fell considerably short of its concentration in the blood. Marshall and Davis² have shown by chemical analyses that the urea concentration in certain organs and tissues of the body is approximately equal to its concentration in the blood. They found, however, that in the case of fat the urea concentration was low, and it seems probable that the same is true of the bones, the cartilages and possibly of other tissues. If one could allow for the low percentages in such

tissues the urea concentration in the remaining tissues of our subjects may have approached that of the blood.

CONCLUSIONS

1. By giving approximately 100 gm. of urea by mouth over a short interval of time it is possible to increase the concentration of urea in the blood of normal persons to levels of from 160 to 245 mg. per 100 c.c.

2. At such levels of blood urea definite symptoms occur. These consist of headache, dizziness, apathy, drowsiness, bodily weakness and fatigue.

3. These symptoms are comparable to those encountered in the asthenic type of uremia.

4. For every gram of excess urea in the body there is a rise of concentration in the blood which approximates 2.5 mg. per 100 c.c.

THE RELATION OF RECURRENT ATTACKS OF PELLAGRA TO RACE, SEX AND AGE OF THE PATIENT AND TO TREATMENT OF THE DISEASE*

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INTRODUCTION

In the immediately preceding papers of this series¹ we have presented a study of the initial attacks of pellagra observed in Spartanburg County, S. C., up to the end of 1914 and a study of the subsequent history of the survivors of the initial attack. In the present paper we purpose to present a study of the correlation between recurrence of the disease, or escape from recurrence, on the one hand, and race, sex and age of the patient and treatment of the disease, on the other hand. It is expected that this study may contribute to the elucidation of the general question of prognosis in pellagra.

THE RELATION OF RECURRENT ATTACKS OF PELLAGRA TO RACE AND SEX

Of the 971 recorded cases of pellagra with onset previous to 1914, there were 157 patients who died in the year of the initial attack, leaving 814 survivors. Of these patients, 521 were white female pellagrins, 218 were white male pellagrins, one was a white child whose sex was not recorded, sixty were colored female and fourteen were colored male pellagrins. Previous to 1908 there were only six recorded cases in negroes, five females and one male. The latter, as well as three of the negro female pellagrins, died during the year of onset. One of the colored females, Pellagrin 406, had her first attack in 1903 and recurrent attacks in 1904, 1905, 1906 and 1907, dying in

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* From the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

* This paper has been written since Dr. Garrison and Dr. Siler were recalled to active duty in the Medical Corps, U. S. Navy and U. S. Army, respectively. They are not personally responsible for the detailed compilation of data or for the specific deductions drawn from them.

1. Siler, Garrison and MacNeal, *THE ARCHIVES INT. MED.*, 1916, xviii, 173; *Ibid.*, 1916, xviii, 340.

1907. The other colored female, Pellagrin 1212, had her first attack in 1905 and recurrent attacks every year to 1911, when she died in a recurrent attack. Table 1 shows the sum of all recurrences, deaths in recurrence, years without recurrence, deaths without recurrence and years without definite record for each annual group of incident cases, according to race and sex, the history of one case for one year being the unit in each instance.

In the group of white female pellagrins there were 1,113 instances in which the record of recurrence or nonrecurrence is clear. Of these 695, or 62.4 per cent., suffered recurrences, and in 418, or 37.6 per cent., there was freedom from recurrence. In the group of white males, out of 445 definite records there were 281, or 63.1 per cent., with recurrence and 164, or 36.9 per cent., without recurrence. The agreement between these two groups in this respect was therefore remarkably close. In the group of colored females, out of ninety-eight instances of definite records in years subsequent to the year of onset, there were sixty-eight recurrences, 69.4 per cent., and thirty instances of freedom from recurrence, or 30.6 per cent. of the total instances of definite record. In the group of colored males, out of fourteen pellagrins with definite records in years subsequent to that of the initial attack, a recurrence was observed in nine, or 64.3 per cent., and freedom from recurrence was observed in five, or 35.7 per cent. The data here tabulated indicate, therefore, that, on the whole, surviving pellagrins in Spartanburg County have suffered recurrences of pellagra in the following years almost twice as frequently as they they have escaped the recurrence, and that there has been no very considerable difference in this respect between the various racial or sex groups. There was, however, a very slightly greater tendency for pellagra to recur in the negro survivors than in the survivors of the white race, the recurrence frequency being 69.4 and 64.3 per cent. for female and male negroes, respectively, as against 62.4 and 63.1 per cent. for female and male whites, respectively. This close agreement is really quite remarkable when compared with the very definite differences in behavior of pellagra in other respects in its relation to race and sex.

The deaths during the year of recurrent attack were sixty-five out of 695 recurrences in white females, representing a death rate of 9.4 per cent., forty-two out of 281 recurrences in white males, a death rate of 14.9 per cent.; for colored females, nineteen deaths in sixty-eight recurrences, a death rate of 27.9 per cent.; for colored males, four deaths in nine recurrences, a death rate of 44.4 per cent. The death rates, therefore, show a marked variation, dependent on race and sex, and this variation is quite similar to that shown by death

TABLE 1.—SUMMARY OF SUBSEQUENT HISTORY OF THE 814 PELLAGRINS WHO SURVIVED THE INITIAL ATTACK, ACCORDING TO RACE AND SEX AND ACCORDING TO YEAR OF ONSET

	Year of Onset							
	Before 1905	1905	1909	1910	1911	1912	1913	Sum
Female, white—								
Incident pellagrins in group.....	39	17	37	93	140	115	154	595
Deaths in year of onset.....	8	2	7	16	18	12	11	74
Survivors of initial attack.....	31	15	30	77	122	103	143	521
Subsequent recurrences	112	45	57	153	178	83	67	695
Deaths in recurrence.....	13	3	9	17	17	4	2	65
Years without recurrence.....	40	20	42	78	121	76	41	418
Deaths without recurrence.....	4	1	2	5	3	4	1	20
Years with uncertain record.....	44	7	15	27	34	37	34	198
Male, white—								
Incident pellagrins in groups.....	12	2	16	30	68	67	59	254
Deaths in year of onset.....	1	0	6	7	6	6	10	36
Survivors of initial attack.....	11	2	10	23	62	61	49	218
Subsequent recurrences	71	8	25	41	60	57	19	281
Deaths in recurrence.....	7	1	4	7	11	11	1	42
Years without recurrence.....	15	0	0	25	72	36	16	164
Deaths without recurrence.....	1	0	1	1	1	1	2	7
Years with uncertain record.....	8	1	7	6	37	21	12	92
Female, colored—								
Incident pellagrins in group.....	5	1	3	15	19	24	25	92
Deaths in year of onset.....	3	0	2	4	6	6	11	32
Survivors of initial attack.....	2	1	1	11	13	18	14	60
Subsequent recurrences	10	6	2	18	17	9	6	68
Deaths in recurrence.....	2	0	1	6	7	3	0	19
Years without recurrence.....	0	0	0	4	10	12	4	30
Deaths without recurrence.....	0	0	0	0	2	2	1	5
Years with uncertain record.....	0	0	0	7	1	9	3	20
Male, colored—								
Incident pellagrins in group.....	1	0	1	3	6	5	13	29
Deaths in year of onset.....	1	0	1	1	3	3	6	15
Survivors of initial attack.....	0	0	0	2	3	2	7	14
Subsequent recurrences	0	0	0	2	3	1	3	9
Deaths in recurrence.....	0	0	0	1	2	0	1	4
Years without recurrence.....	0	0	0	0	3	1	1	5
Deaths without recurrence.....	0	0	0	1	0	1	1	3
Years with uncertain record.....	0	0	0	0	0	0	2	2

rate in the initial attack, considered in a preceding paper of this series. The comparative figures are shown in Table 2. The similarity between death rate in initial attack and death rate in recurrent attack is rather striking. In each instance, except for the group of white males, the death rate in recurrence is slightly lower than the death rate during the year of onset.

TABLE 2.—MORTALITY RATE IN INITIAL ATTACKS AND IN RECURRENT ATTACKS OF PELLAGRA FOR EACH RACE AND SEX, PER CENT., FOR 971 CASES WITH ONSET BEFORE 1914

	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Initial attack.....	12.4	14.2	13	24.8	51.7	28.8	15.4	18	16.2
Recurrent attack.....	9.4	14.9	11	27.9	44.4	29.9	11	15.9	12.3

Attention may be directed to the fact that the white race, in which the incidence of pellagra was much higher, was the one to show the lower death rate in initial attack, lower recurrence rate among survivors and lower death rate in recurrence; furthermore, the females of each race, groups in which the incidence rate of pellagra was relatively much higher than in the males, show the lower death rate in the year of onset, almost equal recurrence rate in subsequent years and lower death rate in recurrence. If, therefore, we consider death rates and recurrence rates to depend on general vigor, condition of nutrition and available diet, it seems somewhat difficult to account for the relative incidence rates without taking into account some additional factor.

RELATION BETWEEN RECURRENCE AND AGE AT ONSET OF PELLAGRA

In our series of 1,180 cases of pellagra there were fourteen with onset of the disease before the age of 2 years had been attained. These cases have been fully considered in the fifth paper of this series² in which their histories were presented in detail. Of the fourteen patients, one, the only negro in the group, died in the initial attack of pellagra. Five of the little pellagrins were white girls, three with onset of pellagra in 1914, one with onset in 1909 and one in 1911. The latter died early in 1912 without recurrence. The former suffered recurrence in 1910, the second year, and escaped without recurrence in 1911, 1912, 1913 and 1914. Eight of the pellagrous infants were white boys, six of them with onset before 1914. The subsequent

2. Footnote 1, first reference.

TABLE 3.—SUMMARY OF THE SUBSEQUENT HISTORY OF THE 814 PELLAGRINS WHO SURVIVED THE YEAR OF INITIAL ATTACK PREVIOUS TO 1914

Age at Onset, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Subsequent years with recurrence:									
0 to 4.....	26	23	49	0	0	0	26	23	49
5 to 9.....	23	28	51	4	0	4	27	28	55
10 to 14.....	11	7	18	0	0	0	11	7	18
15 to 19.....	66	5	71	10	2	12	76	7	83
20 to 29.....	276	15	291	24	5	29	300	20	320
30 to 39.....	161	46	207	21	1	22	182	47	229
40 to 49.....	77	47	124	6	0	6	83	47	130
50 to 59.....	43	59	102	1	1	2	44	60	104
60 to 69.....	8	45	53	0	0	0	8	45	53
Over 70.....	1	6	7	0	0	0	1	6	7
Age unknown.....	3	0	3	2	0	2	5	0	5
Total.....	695	281	976	68	9	79	763	290	1,053
Deaths in year of recurrence:									
0 to 4.....	0	1	1	0	0	0	0	1	1
5 to 9.....	1	1	2	1	0	1	2	1	3
10 to 14.....	0	0	0	0	0	0	0	0	0
15 to 19.....	6	0	6	4	1	5	10	1	11
20 to 29.....	24	3	27	6	1	7	30	4	34
30 to 39.....	16	6	22	3	1	4	19	7	26
40 to 49.....	9	13	22	1	0	1	10	13	23
50 to 59.....	7	11	18	3	1	4	10	12	22
60 to 69.....	1	4	5	0	0	0	1	4	5
Over 70.....	0	3	3	0	0	0	0	3	3
Age unknown.....	1	0	1	1	0	1	2	0	2
Total.....	65	42	107	19	4	23	84	46	130
Years survived without recurrence:									
0 to 4.....	28	39	67	0	0	0	28	39	67
5 to 9.....	28	26	54	0	0	0	28	26	54
10 to 14.....	7	20	27	0	0	0	7	20	27
15 to 19.....	31	6	37	6	0	6	37	6	43
20 to 29.....	128	4	132	18	1	19	146	5	151
30 to 39.....	113	15	128	3	0	3	116	15	131
40 to 49.....	72	30	102	1	4	5	73	34	107
50 to 59.....	7	19	26	0	0	0	7	19	26
60 to 69.....	3	5	8	0	0	0	3	5	8
Over 70.....	1	0	1	2	0	2	3	0	3
Age unknown.....	0	0	0	0	0	0	0	0	0
Total.....	418	164	582	30	5	35	448	169	617

TABLE 3.—SUMMARY OF THE SUBSEQUENT HISTORY OF THE 814 PELLAGRINS WHO SURVIVED THE YEAR OF INITIAL ATTACK PREVIOUS TO 1914—(Continued)

Age at Onset, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
Deaths without recurrence in year of death:									
0 to 4.....	1	0	1	0	0	0	1	0	0
5 to 9.....	0	0	0	0	1	1	0	1	1
10 to 14.....	0	0	0	0	0	0	0	0	0
15 to 19.....	2	0	2	0	0	0	2	0	2
20 to 29.....	8	1	9	1	0	1	9	1	10
30 to 39.....	4	0	4	0	1	1	4	1	5
40 to 49.....	1	1	2	0	0	0	1	1	2
50 to 59.....	2	2	4	3	0	3	5	2	7
60 to 69.....	1	2	2	1	1	2	2	2	5
Over 70.....	1	1	2	0	0	0	1	1	2
Age unknown.....	0	0	0	0	0	0	0	0	0
Total.....	20	7	27	5	3	8	25	10	35
Years without definite record:									
0 to 4.....	5	9	17*	0	0	0	5	9	17*
5 to 9.....	6	15	21	2	1	3	8	16	24
10 to 14.....	2	9	11	0	0	0	2	9	11
15 to 19.....	15	6	21	1	0	1	16	6	22
20 to 29.....	68	9	77	10	0	10	78	9	87
30 to 39.....	51	12	63	6	0	6	57	12	69
40 to 49.....	24	10	34	1	0	1	25	10	35
50 to 59.....	13	19	32	0	0	0	13	19	32
60 to 69.....	5	2	8	0	1	1	5	4	9
Over 70.....	0	0	0	0	0	0	0	0	0
Age unknown.....	9	0	9	0	0	0	9	0	9
Total.....	193	62	255*	29	2	31	218	64	282*

* Including the record of one white child, sex unknown, with initial attack in 1911 and indefinite record in 1912, 1913 and 1914.

history of these six patients shows eleven instances of recurrence, one instance of death in recurrence and eight instances of a year without recurrence. The subsequent history of the whole group showed, therefore, twelve instance of recurrence, one instance of death in recurrence, twelve instances of survival of a year without recurrence and one death in a year without recurrence.

There were seventy-two pellagrins, 2 to 4 years of age at the time of onset of the disease, of whom fifty-six had the initial attack before 1914, with two deaths during the year of onset. The subsequent history of the fifty-four remaining patients is summarized along with that of the cases with onset under the age of 2 years in Table 3. In

this table are presented the summarized data in regard to subsequent history for the 814 survivors of the initial attack, according to race, sex and age at onset of the disease, by 5-year age periods to age 20, and after that by decades. There are 521 white females, 218 white males, one white child of unknown sex, sixty negro females and fourteen negro males here considered. The important sections of this table are those showing the years with recurrence, the deaths in recurrence and the number of escapes from recurrence. The data for deaths in a year without recurrence and for years without definite record are also presented in the table for the sake of completeness. The number of these is roughly proportional to the size of the respective groups of survivors of the initial attack. The influence of age at onset on recurrence in subsequent years may be seen by comparing the number of recurrences with the total instances of definite record (that is, the sum of recurrences and escapes from recurrence) shown in the record of each age group and by computing the death rate for the recurrences in each age group. The relative frequency of recurrence for each age group is shown in Table 4. The tendency to recurrence in subsequent years has been distinctly less in white children than in the white adults. The variation between the different groups in this respect is somewhat irregular, but the white girls under 10 years of age at onset of the disease furnished forty-nine instances of recurrence in a total of 105 definite observations, or 46.7 per cent., while in the group with onset between 10 and 20 years of age the recurrences were seventy-seven in a total of 115 definite observations, or 67 per cent., and in the large group of white women with onset of pellagra in the age period from 20 to 59 years, the subsequent record showed 557 recurrences out of 877 definite observations, or 63.5 per cent., so that the prognosis for escape from recurrence was distinctly better in children than in adults. For the white males this distinction between children and adults is even more marked. Of the 116 definite observations in subsequent years for boys who contracted pellagra before the age of 10, only fifty-one were instances of recurrence, or 44 per cent., while the 235 definite records for subsequent years for the men who contracted pellagra between the ages of 20 and 50 years, include 167 instances of recurrence, or 71.1 per cent. The very low recurrence rate (25.9 per cent.) for boys between 10 and 15 years of age at the time of onset is in accord with the evidence previously presented, indicating an increased resistance to pellagra becoming manifest at about this time and continuing for several years in the male sex. For the white women who contracted pellagra after the age of 60 years and survived the year of onset, there were thirteen instances of definite observation in a subsequent year, of which nine

were recurrences and four were escapes from recurrence. The recurrence rate was therefore 69.2 per cent., slightly higher than in the younger women. The white men who contracted pellagra after the age of 60 years furnished fifty-six instances of definite record in sub-

TABLE 4.—RELATIVE FREQUENCY OF RECURRENCE OF PELLAGRA IN THE DEFINITE RECORDS OF THE 814 PELLAGRINS WHO SURVIVED THE INITIAL ATTACK OF PELLAGRA PREVIOUS TO 1914, GROUPED ACCORDING TO RACE, SEX AND AGE AT ONSET OF INITIAL ATTACK

Age at Onset of Initial Attack	Female			Male			Both Sexes		
	Total Definite Records	Recurrences		Total Definite Records	Recurrences		Total Definite Records	Recurrences	
		Number	Per Cent.		Number	Per Cent.		Number	Per Cent.
White pellagrins									
0 to 4.....	54	26	48.1	62	23	37.1	116	49	42.2
5 to 9.....	51	23	45.1	54	28	51.9	105	51	48.6
10 to 14.....	18	11	61.1	27	7	25.9	45	18	40
15 to 19.....	97	66	68	11	5	45.5	108	71	65.7
20 to 29.....	404	276	68.3	19	15	78.9	423	291	68.8
30 to 39.....	274	161	58.8	61	46	75.4	335	207	61.8
40 to 49.....	149	77	51.7	77	47	61	226	124	54.9
50 to 59.....	50	42	86	78	59	75.6	128	102	79.7
60 to 69.....	11	8	72.7	50	45	90	61	53	86.9
Over 70.....	2	1	50	6	6	100	8	7	87.5
Age unknown...	3	3	100	0	0	3	3	100
Total.....	1,113	695	62.4	445	281	63.1	1,558	976	62.6
Colored pellagrins									
0 to 4.....	0	0	0	0	0	0
5 to 9.....	4	4	100	0	0	4	4	100
10 to 14.....	0	0	0	0	0	0
15 to 19.....	16	10	62.5	2	2	100	18	12	66.7
20 to 29.....	42	24	57.1	6	5	83.3	48	29	60.4
30 to 39.....	24	21	87.5	1	1	100	25	22	88
40 to 49.....	7	6	85.7	4	0	0	11	6	54.5
50 to 59.....	1	1	100	1	1	100	2	2	100
60 to 69.....	0	0	0	0	0	0
Over 70.....	2	0	0	0	0	2	0	0
Age unknown...	2	2	100	0	0	2	2	100
Total.....	98	68	69.4	14	9	64.3	112	77	68.8
Total both races.	1,211	763	63.0	459	290	63.2	1,670	1,053	63.1

sequent years, fifty-one of which were recurrences and only five escapes from recurrence. The indicated recurrence rate, 91.1 per cent., is considerably higher than for the younger men.

The figures in regard to tendency for pellagra to recur in the colored pellagrins are of much less value because of the smaller number of observations in this race. On the whole, they seem to be not significantly different from those for the white race.

TABLE 5.—DEATH RATE IN RECURRENT ATTACKS OF PELLAGRA FOR EACH GROUP ACCORDING TO RACE, SEX AND AGE AT ONSET OF THE INITIAL ATTACK

Age at Onset of Initial Attack	Female			Male			Both Sexes		
	Recur- rent Attacks	Deaths	Rate per Cent.	Recur- rent Attacks	Deaths	Rate per Cent.	Recur- rent Attacks	Deaths	Rate per Cent.
White pellagrins									
0 to 4.....	26	0	0	23	1	4.3	49	1	2
5 to 9.....	23	1	4.3	28	1	3.6	51	2	3.9
10 to 14.....	11	0	0	7	0	0	18	0	0
15 to 19.....	66	6	9.1	5	0	0	71	6	8.5
20 to 29.....	276	24	8.7	15	3	20	291	27	9.3
30 to 39.....	161	16	9.9	46	6	13	207	22	10.6
40 to 49.....	77	9	11.7	47	13	27.7	124	22	17.7
50 to 59.....	43	7	16.3	59	11	18.6	102	18	17.6
60 to 69.....	8	1	12.5	45	4	8.8	53	5	9.4
Over 70.....	1	0	0	6	3	50	7	3	42.9
Age unknown...	3	1	33.3	0	0	3	1	33.3
Total.....	695	65	9.4	281	42	14.9	976	107	11
Colored pellagrins									
0 to 4.....	0	0	0	0	0	0
5 to 9.....	4	1	25	0	0	4	1	25
10 to 14.....	0	0	0	0	0	0
15 to 19.....	10	4	40	2	1	50	12	5	41.7
20 to 29.....	24	6	25	5	1	20	29	7	24.1
30 to 39.....	21	3	14.3	1	1	100	22	4	18.2
40 to 49.....	2	1	50	0	0	2	1	50
50 to 59.....	5	3	60	1	1	100	6	4	66.7
60 to 69.....	0	0	0	0	0	0
Over 70.....	0	0	0	0	0	0
Age unknown...	2	1	50	0	0	2	1	50
Total.....	68	19	27.9	9	4	44.4	79	23	29.1

The death rate in the known recurrences for each group of pellagrins according to age at onset of the initial attack is shown in Table 5. The better prognosis in children is also apparent here in the relatively low mortality in recurrent attack for those under 10 years of age at the onset of pellagra. There were just 100 recorded recurrent attacks in the white children of this age group with only three deaths.

The increased resistance to pellagra at puberty is again indicated by the eighteen recurrences in the group with onset at age 10 to 14, inclusive, with no deaths at all. For those with onset at later years of life the mortality rate in recurrence increases with their age at onset, although irregular fluctuations are present. In the 557 recurrent attacks in white women with onset of pellagra between 20 to 60 years, there were fifty-six deaths, the indicated mortality rate being 10.1 per cent. In the analogous group of white men there were thirty-three deaths in 167 recurrent attacks, indicating a death rate of 19.8 per cent. In the analogous age group of negro women there were thirteen deaths in fifty-two recurrent attacks, a death rate of 25 per cent., and in the similar age group of colored men the death rate was 42.9 per cent., three deaths in seven recurrent attacks. The negro children furnished only four recorded recurrences, all in girls, with one death.

THE RELATION OF SEX AND AGE TO RECOVERY FROM PELLAGRA

A reliable criterion by which to judge recovery from pellagra is not known to us. It nevertheless seems worth while to consider those pellagrins who suffered their initial attack in 1912 or before and have remained free from any recurrence of the disease for two or more years as instances of probable recovery. As has been shown in the preceding paper of this series, it may be expected that a few of these are not really valid recoveries and it will be evident from what follows here that this statement applies especially to the child-bearing women. Nevertheless, a period of at least two years without any recurrence is a definite and sufficiently accurate criterion of recovery for our present purpose, which is to show the relation of recovery to race, sex and age.

The distribution, according to sex and age at onset of the initial attack, of the white pellagrins in this category is shown in Table 6. The significance of these figures will be better appreciated by comparing them with the number of incident attacks of pellagra observed at each age in the years previous to 1913, shown in the fifth paper² of this series. This comparison is shown in Table 7 for the 5-year age groups. The tendency to recovery after one attack is distinctly greater in children, no less than thirty, or 34.9 per cent., of the eighty-six pellagrins with onset under the age of 10 years having suffered only the single attack. Of the twelve boys who had their first attack of pellagra in the age period 10 to 14 years, no less than six, or 50 per cent., escaped recurrence of the disease. Of the 478 white pellagrins with onset after the age of 20 years, previous to 1913, only forty-three have remained free from recurrence, giving a recovery

TABLE 6.—WHITE PELLAGRINS WHO SUFFERED ONLY ONE ATTACK AND HAVE REMAINED FREE FROM RECURRENCE FOR AT LEAST TWO YEARS

Age at Onset	Female	Male	Total	Age at Onset	Female	Male	Total
0	0	0	0	30	2	0	2
1	0	2	2	31	0	0	0
2	2	2	4	32	1	2	3
3	2	1	3	33	2	1	3
4	3	4	7	34	2	0	2
5	1	1	2	35	2	0	2
6	2	4	6	36	0	0	0
7	1	0	1	37	1	0	1
8	2	1	3	38	1	1	2
9	1	1	2	39	1	0	1
10	1	1	2	40	1	0	1
11	0	1	1	41	2	0	2
12	0	1	1	42	2	2	4
13	1	1	2	43	1	0	1
14	0	2	2	44	0	0	0
15	0	0	0	45	1	0	1
16	0	0	0	46	1	0	1
17	3	2	5	47	1	0	1
18	0	0	0	48	0	0	0
19	1	0	1	49	0	0	0
20	1	0	1	50	0	0	0
21	0	0	0	51	0	0	0
22	2	0	2	52	0	0	0
23	2	1	3	53	0	0	0
24	1	0	1	54	0	0	0
25	1	0	1	55	0	1	1
26	2	0	2	56	0	0	0
27	2	0	2	57	0	1	1
28	0	0	0				
29	2	0	2				
				Total....	54	33	87

TABLE 7.—PROPORTION OF WHITE PELLAGRINS WITH ONSET BEFORE 1913, WHO HAVE SUFFERED NO RECURRENCE, DISTRIBUTED ACCORDING TO SEX AND AGE AT ONSET OF THE INITIAL ATTACK

Age at Onset, Years	White Female			White Male			Total White		
	Incident Pella-grins	Without Recurrence		Incident Pella-grins	Without Recurrence		Incident Pella-grins	Without Recurrence	
		Number	Per Cent.		Number	Per Cent.		Number	Per Cent.
0 to 4.....	18	7	38.9	22	9	40.9	41†	16	39
5 to 9.....	20	7	35	23	7	30.4	43	14	32.6
10 to 14.....	9	2	22.2	12	6	50	21	8	38.1
15 to 19.....	37	4	10.8	5	2	40	42	6	14.3
20 to 29.....	135*	13	9.6	13	1	7.7	148*	14	9.5
30 to 39.....	111	12	10.8	24	4	16.7	135	16	11.9
40 to 49.....	57	9	15.8	35	2	5.7	92	11	12
50 to 59.....	30	0	0	37	2	5.4	67	2	3
60 to 69.....	14	0	0	15	0	0	29	0	0
Over 70.....	1	0	0	6	0	0	7	0	0
Age unknown...	10	0	0	2	0	0	12	0	0
Total.....	442*	54	12.2	194	33	17	637*	87	13.7

* Excluding Pellagrin 789, a colored female, who was included in the group of white females by mistake in the fifth paper of this series.

† Including a white child, aged 2 years, whose sex was not ascertained.

rate of 9 per cent. According to this analysis the chance of recovery after one attack is about four times as good in white children under 10 years of age as in white adults over the age of 20 years.

It seems useless to tabulate the data in regard to similar recoveries in negroes, because there are only seven instances in this race. Six of them were colored women with onset at the ages of 18, 20, 22, 22, 23 and 29, and one was a colored man with onset at the age of 48 years.

In a previous paper³ we have called attention to the recurrence of pellagra after an interval of freedom from attacks of the disease, but in that study it was evident that escape for one year made subsequent recurrence rather unlikely. Among the 720 pellagrins with initial attack previous to 1913, there were twenty-four who escaped recurrence for one year only to suffer recurrence in the following year. Two of these were colored women, ages at onset of initial attack

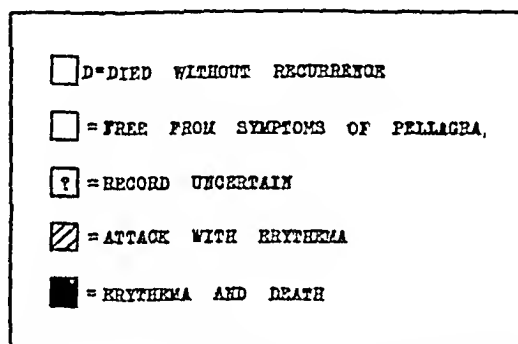


Fig. 1.—Key for the interpretation of Figures 2, 3, 4 and 5.

being 25 years and 34 years. Four were white males, ages at onset of the initial attack being 14, 44, 54 and 56 years. Eighteen were white females, the ages at onset being 5, 7, 16, 21, 22, 24, 24, 26, 26, 26, 30, 30, 32, 34, 35, 36, 39 and 42 years.

Among the 509 pellagrins with initial attack previous to 1912, there were fourteen who escaped recurrence for two consecutive years and then suffered recurrence in the next year. All of them were white females and their ages at onset were 7, 22, 23, 23, 25, 28, 28, 29, 32, 33, 33, 34, 37 and 44 years. The great excess of white women of the child-bearing age in such instances of escape for one or two years with subsequent recurrence suggests that pregnancy and childbirth have an important relation to the phenomenon. We expect to discuss this relationship in a subsequent paper of this series.

In the series of pellagrins there were instances of recurrence (or of new onset?) after much longer intervals of freedom from attack, the longest interval of good health being eighteen years. These instances are not sufficiently numerous to warrant detailed discussion.

Figures 1, 2, 3, 4 and 5 show in detail the behavior during subse-

3. Footnote 1, second reference.

TABLE 6.—WHITE PELLAGRINS WHO SUFFERED ONLY ONE ATTACK AND HAVE REMAINED FREE FROM RECURRENCE FOR AT LEAST TWO YEARS

Age at Onset	Female	Male	Total	Age at Onset	Female	Male	Total
0	0	0	0	30	2	0	2
1	0	2	2	31	0	0	0
2	2	2	4	32	1	2	3
3	2	1	3	33	2	1	3
4	3	4	7	34	2	0	2
5	1	1	2	35	2	0	2
6	2	4	6	36	0	0	0
7	1	0	1	37	1	0	1
8	2	1	3	38	1	1	2
9	1	1	2	39	1	0	1
10	1	1	2	40	1	0	1
11	0	1	1	41	2	0	2
12	0	1	1	42	2	2	4
13	1	1	2	43	1	0	1
14	0	2	2	44	0	0	0
15	0	0	0	45	1	0	1
16	0	0	0	46	1	0	1
17	3	2	5	47	1	0	1
18	0	0	0	48	0	0	0
19	1	0	1	49	0	0	0
20	1	0	1	50	0	0	0
21	0	0	0	51	0	0	0
22	2	0	2	52	0	0	0
23	2	1	3	53	0	0	0
24	1	0	1	54	0	0	0
25	1	0	1	55	0	1	1
26	2	0	2	56	0	0	0
27	2	0	2	57	0	1	1
28	0	0	0				
29	2	0	2				
				Total....	54	33	87

TABLE 7.—PROPORTION OF WHITE PELLAGRINS WITH ONSET BEFORE 1913, WHO HAVE SUFFERED NO RECURRENCE, DISTRIBUTED ACCORDING TO SEX AND AGE AT ONSET OF THE INITIAL ATTACK

Age at Onset, Years	White Female			White Male			Total White		
	Incident Pellagrins	Without Recurrence		Incident Pellagrins	Without Recurrence		Incident Pellagrins	Without Recurrence	
		Number	Per Cent.		Number	Per Cent.		Number	Per Cent.
0 to 4.....	18	7	38.9	22	9	40.9	41†	16	39
5 to 9.....	20	7	35	23	7	30.4	43	14	32.6
10 to 14.....	9	2	22.2	12	6	50	21	8	38.1
15 to 19.....	37	4	10.8	5	2	40	42	6	14.3
20 to 29.....	135*	13	9.6	13	1	7.7	148*	14	9.5
30 to 39.....	111	12	10.8	24	4	16.7	135	16	11.9
40 to 49.....	57	9	15.8	35	2	5.7	92	11	12
50 to 59.....	30	0	0	37	2	5.4	67	2	3
60 to 69.....	14	0	0	15	0	0	29	0	0
Over 70.....	1	0	0	6	0	0	7	0	0
Age unknown...	10	0	0	2	0	0	12	0	0
Total.....	442*	54	12.2	194	33	17	637*	87	13.7

* Excluding Pellagrin 789, a colored female, who was included in the group of white females by mistake in the fifth paper of this series.
† Including a white child, aged 2 years, whose sex was not ascertained.

rate of 9 per cent. According to this analysis the chance of recovery after one attack is about four times as good in white children under 10 years of age as in white adults over the age of 20 years.

It seems useless to tabulate the data in regard to similar recoveries in negroes, because there are only seven instances in this race. Six of them were colored women with onset at the ages of 18, 20, 22, 22, 23 and 29, and one was a colored man with onset at the age of 48 years.

In a previous paper³ we have called attention to the recurrence of pellagra after an interval of freedom from attacks of the disease, but in that study it was evident that escape for one year made subsequent recurrence rather unlikely. Among the 720 pellagrins with initial attack previous to 1913, there were twenty-four who escaped recurrence for one year only to suffer recurrence in the following year. Two of these were colored women, ages at onset of initial attack

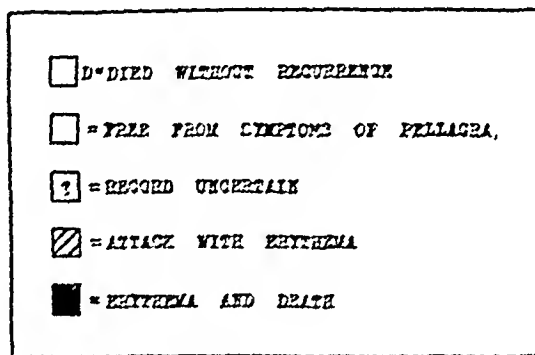


Fig. 1.—Key for the interpretation of Figures 2, 3, 4 and 5.

being 25 years and 34 years. Four were white males, ages at onset of the initial attack being 14, 44, 54 and 56 years. Eighteen were white females, the ages at onset being 5, 7, 16, 21, 22, 24, 24, 26, 26, 26, 30, 30, 32, 34, 35, 36, 39 and 42 years.

Among the 509 pellagrins with initial attack previous to 1912, there were fourteen who escaped recurrence for two consecutive years and then suffered recurrence in the next year. All of them were white females and their ages at onset were 7, 22, 23, 23, 25, 28, 28, 29, 32, 33, 33, 34, 37 and 44 years. The great excess of white women of the child-bearing age in such instances of escape for one or two years with subsequent recurrence suggests that pregnancy and childbirth have an important relation to the phenomenon. We expect to discuss this relationship in a subsequent paper of this series.

In the series of pellagrins there were instances of recurrence (or of new onset?) after much longer intervals of freedom from attack, the longest interval of good health being eighteen years. These instances are not sufficiently numerous to warrant detailed discussion.

Figures 1, 2, 3, 4 and 5 show in detail the behavior during subse-

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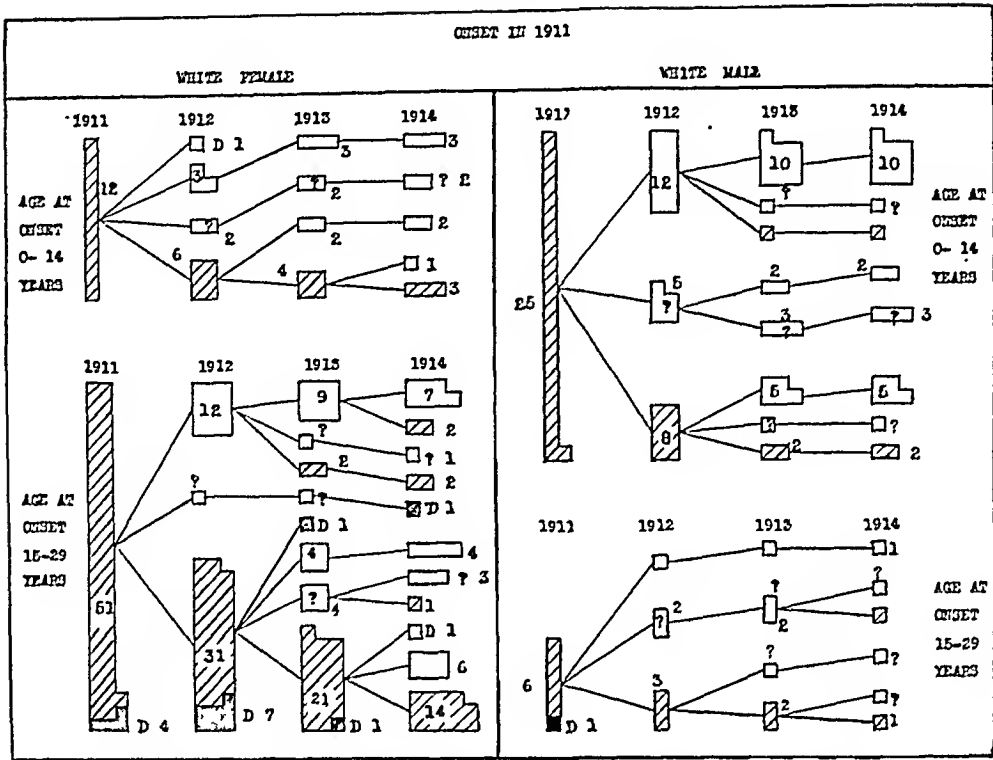


Fig. 2.—Behavior of white pellagrins who suffered their initial attacks of pellagra in 1911 before attaining the age of 30 years, grouped according to sex and age at onset of the initial attack.

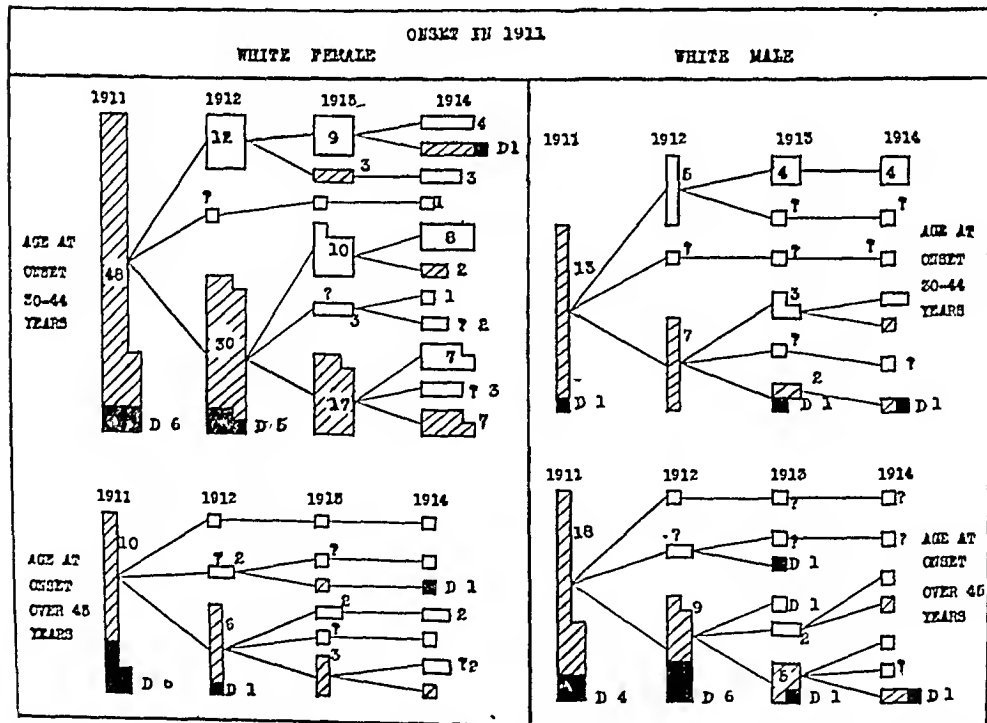


Fig. 3.—Behavior of white pellagrins who suffered their initial attacks of pellagra in 1911 after attaining the age of 30 years, grouped according to sex and age at onset of the initial attack.

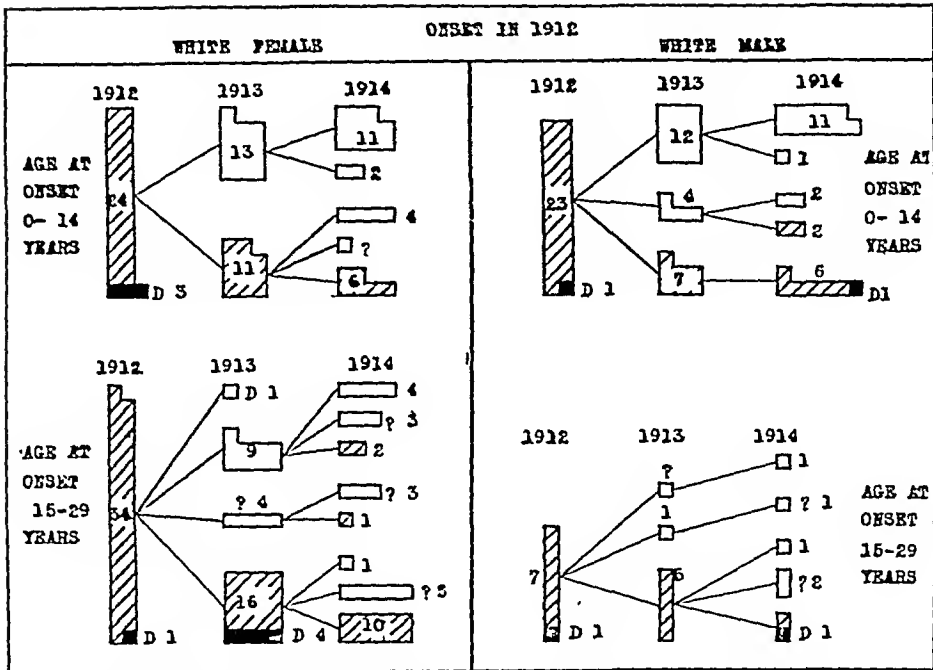


Fig. 4.—Behavior of white pellagrins who suffered their initial attacks of pellagra in 1912 before attaining the age of 30 years, grouped according to sex and age at onset of the initial attack. In the upper groups of this figure are represented two girls and one boy who escaped recurrence in 1913 and were without definite record in 1914. The question mark has been omitted in the 1914 blocks by mistake.

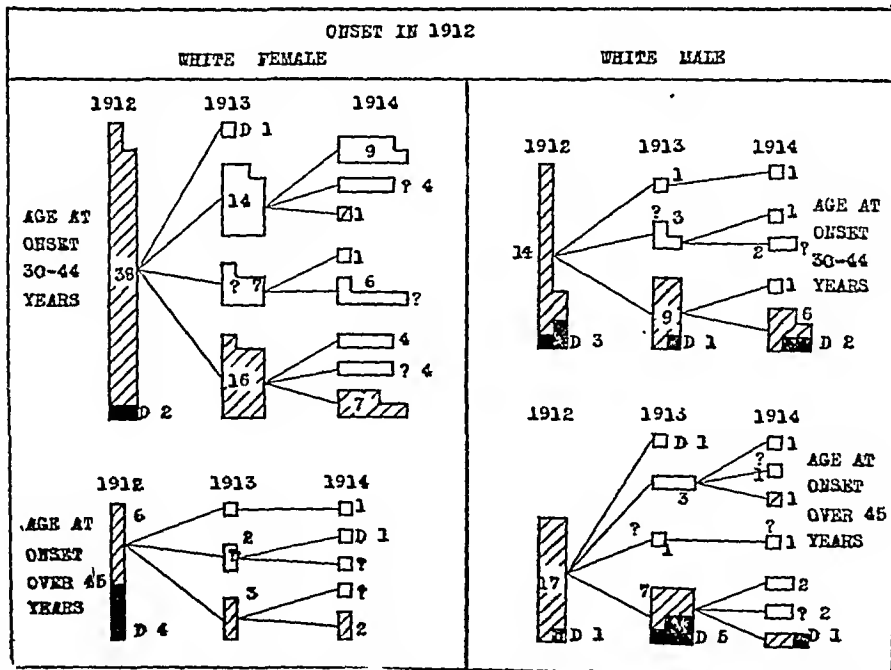


Fig. 5.—Behavior of white pellagrins who suffered their initial attacks of pellagra in 1912 after attaining the age of 30 years, grouped according to sex and age at onset of the initial attack.

quent years of the white pellagrins who suffered their first attacks in 1911 and 1912, by 15-year age groups. These figures indicate more definitely than do the tables the exact nature of the records. Especially noticeable is the low death rate in recurrence for the pellagrins who had their initial attack before the age of 15 and the considerable number of apparent recoveries in these groups. One should also note in the white women of child-bearing age a marked tendency to recurrence after escaping an attack for one year or even longer, which is not so evident in the other groups. The higher death rate in older men is also evident.

THE BETTER PROGNOSIS OF PELLAGRA IN CHILDREN

Table 8 presents in a summarized form for easy comparison the incidence rate of pellagra per 10,000 population, the death rate in year of initial attack, the rate of recovery after one attack, the recurrence rate of the survivors in subsequent years and the death rate in recurrent attack for the white children with onset of pellagra under the age of 10 and for the total white population. The contrast indicates very distinctly the much better prognosis in children, especially in respect to death rate and recovery rate, although they contracted the disease almost as readily as the rest of the population. The contrast is especially definite in the white males, in which group the children show an incidence rate approximately equal to that of the whole group, but their death rate in the year of onset is about one twentieth, their recovery rate more than twice, their recurrence rate a little more than two-thirds and their mortality in recurrence about one fourth that of the whole group.

TABLE 8.—COMPARISON OF WHITE CHILDREN WITH ONSET OF PELLAGRA UNDER 10 YEARS, WITH TOTAL WHITE PELLAGROUS POPULATION IN RESPECT TO INCIDENCE RATE, DEATH RATE IN YEAR OF ONSET, RECOVERY RATE, RECURRENCE RATE AND DEATH RATE IN RECURRENCE OF PELLAGRA

	White Female		White Male		Both Sexes	
	Children	Total Population	Children	Total Population	Children	Total Population
Incidence* per 10,000..	102	231	101	103	102	165
Deaths* in initial attack, per cent.	2.3	11.7	1.1	21.2	1.7	14.1
Recovery after one attack, per cent. ...	36.8	12.2	35.6	17	35.7	13.7
Recurrence rate, per cent.	46.7	62.4	44	63.1	45.2	62.6
Deaths in recurrence, per cent.	2	9.4	3.9	14.9	3	11

* Detailed data will be found in a preceding paper of this series, *THE ARCHIVES INT. MED.*, 1916, xviii, 173.

TABLE 9.—THE DISTRIBUTION OF THE TOTAL 1,053 RECURRENT ATTACKS OF PELLAGRA ACCORDING TO AGE OF THE PATIENT AT ONSET OF THE RESPECTIVE RECURRENCE

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0.....	0	0	0	0	0	0	0	0	0
1.....	0	2	2	0	0	0	0	2	2
2.....	1	4	5	0	0	0	1	4	5
3.....	3	8	11	0	0	0	3	8	11
4.....	5	3	8	0	0	0	5	3	8
5.....	11	5	16	0	0	0	11	5	16
6.....	6	3	9	0	0	0	6	3	9
7.....	4	6	10	1	0	1	5	6	11
8.....	6	8	14	0	0	0	6	8	14
9.....	6	6	12	0	0	0	6	6	12
10.....	7	4	11	0	0	0	7	4	11
11.....	2	4	6	0	0	0	2	4	6
12.....	2	2	4	1	0	1	3	2	5
13.....	4	1	5	0	0	0	4	1	5
14.....	2	0	2	0	0	0	2	0	2
15.....	1	0	1	0	0	0	1	0	1
16.....	1	2	3	1	0	1	2	2	4
17.....	5	1	6	1	0	1	6	1	7
18.....	10	0	10	2	1	3	12	1	13
19.....	14	0	14	2	1	3	16	1	17
20.....	17	2	19	4	0	4	21	2	23
21.....	16	1	17	1	0	1	17	1	18
22.....	21	2	23	2	2	4	23	4	27
23.....	20	2	22	2	2	4	22	4	26
24.....	24	1	25	2	0	2	26	1	27
25.....	24	0	24	4	0	4	28	0	28
26.....	37	3	40	4	1	5	41	4	45
27.....	37	3	40	2	0	2	39	3	42
28.....	37	2	39	2	0	2	39	2	41
29.....	30	1	31	2	0	2	32	1	33
30.....	24	2	26	2	0	2	26	2	28
31.....	16	0	16	6	0	6	22	0	22
32.....	21	1	22	2	0	2	23	1	24
33.....	20	3	23	2	0	2	22	3	25
34.....	19	3	22	3	1	4	22	4	26
35.....	23	4	27	4	0	4	27	4	31
36.....	20	5	25	3	0	3	23	5	28
37.....	17	6	23	1	0	1	18	6	24
38.....	20	8	28	1	0	1	21	8	29
39.....	8	5	13	1	0	1	9	5	14
40.....	11	4	15	1	0	1	12	4	16
41.....	9	4	13	0	0	0	9	4	13
42.....	11	6	17	1	0	1	12	6	18
43.....	13	5	18	0	0	0	13	5	18
44.....	6	7	13	0	0	0	6	7	13
45.....	13	9	22	0	0	0	13	9	22
46.....	4	1	5	0	0	0	4	1	5
47.....	4	3	7	0	0	0	4	3	7
48.....	4	5	9	0	0	0	4	5	9
49.....	5	3	8	0	0	0	5	3	8
50.....	8	5	13	1	0	1	9	5	14
51.....	7	2	9	0	0	0	7	2	9
52.....	10	3	12	0	0	0	10	3	13
53.....	3	4	7	0	0	0	3	4	7
54.....	6	3	9	2	0	2	8	3	11
55.....	5	5	10	0	0	0	5	5	10
56.....	6	5	11	0	0	0	6	5	11
57.....	3	5	8	1	0	1	4	5	9
58.....	4	8	12	1	1	2	5	9	14
59.....	2	8	10	0	0	0	2	8	10

TABLE 9.—THE DISTRIBUTION OF THE TOTAL 1,053 RECURRENT ATTACKS OF PELLAGRA ACCORDING TO AGE OF THE PATIENT AT ONSET OF THE RESPECTIVE RECURRENCE—(Continued)

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60.....	3	9	12	1	0	1	4	9	13
61.....	3	6	9	0	0	0	3	6	9
62.....	2	5	7	0	0	0	2	5	7
63.....	1	6	7	0	0	0	1	6	7
64.....	1	5	6	0	0	0	1	5	6
65.....	2	7	9	0	0	0	2	7	9
66.....	2	1	3	0	0	0	2	1	3
67.....	2	1	3	0	0	0	2	1	3
68.....	0	1	1	0	0	0	0	1	1
69.....	0	3	3	0	0	0	0	3	3
70.....	0	4	4	0	0	0	0	4	4
71.....	0	4	4	0	0	0	0	4	4
72.....	0	3	3	0	0	0	0	3	3
73.....	0	3	3	0	0	0	0	3	3
74.....	0	2	2	0	0	0	0	2	2
75.....	0	3	3	0	0	0	0	3	3
76.....	0	3	3	0	0	0	0	3	3
77.....	0	1	1	0	0	0	0	1	1
78.....	1	1	2	0	0	0	1	1	2
79.....	0	2	2	0	0	0	0	2	2
80.....	0	1	1	0	0	0	0	1	1
81.....	0	1	1	0	0	0	0	1	1
82.....	0	1	1	0	0	0	0	1	1
Total age known	692	281	973	66	9	75	758	290	1,048
Age unknown....	3	0	3	2	0	2	5	0	5
Total.....	695	281	976	68	9	77	763	290	1,053

THE AGE OF PELLAGRINS AT THE TIME OF RECURRENT ATTACKS OF THE DISEASE

In the preceding discussion we have grouped the pellagrins according to their age at the onset of the initial attack. We wish further to consider their behavior in each subsequent year in relation to their age in the year of observation. The point of view is a little different; for example, a pellagrin with onset of the disease in 1911, at the age of 4 years, with recurrence in 1912, 1913 and 1914, has furnished three recurrences to the age group with onset under 5 years in the above discussion. The recurrences appeared, however, when the patient was 5 years, 6 years and 7 years old, respectively. We shall now pay particular attention to the age at the time of recurrence or escape from recurrence.

For the 814 pellagrins who survived the initial attack in a year previous to 1914, there are 1,053 recorded instances of recurrence in a subsequent year, all the events of a single year being counted as one unit recurrence. The distribution of these 1,053 recurrent attacks according to race, sex and age at onset of the recurrent erythema is

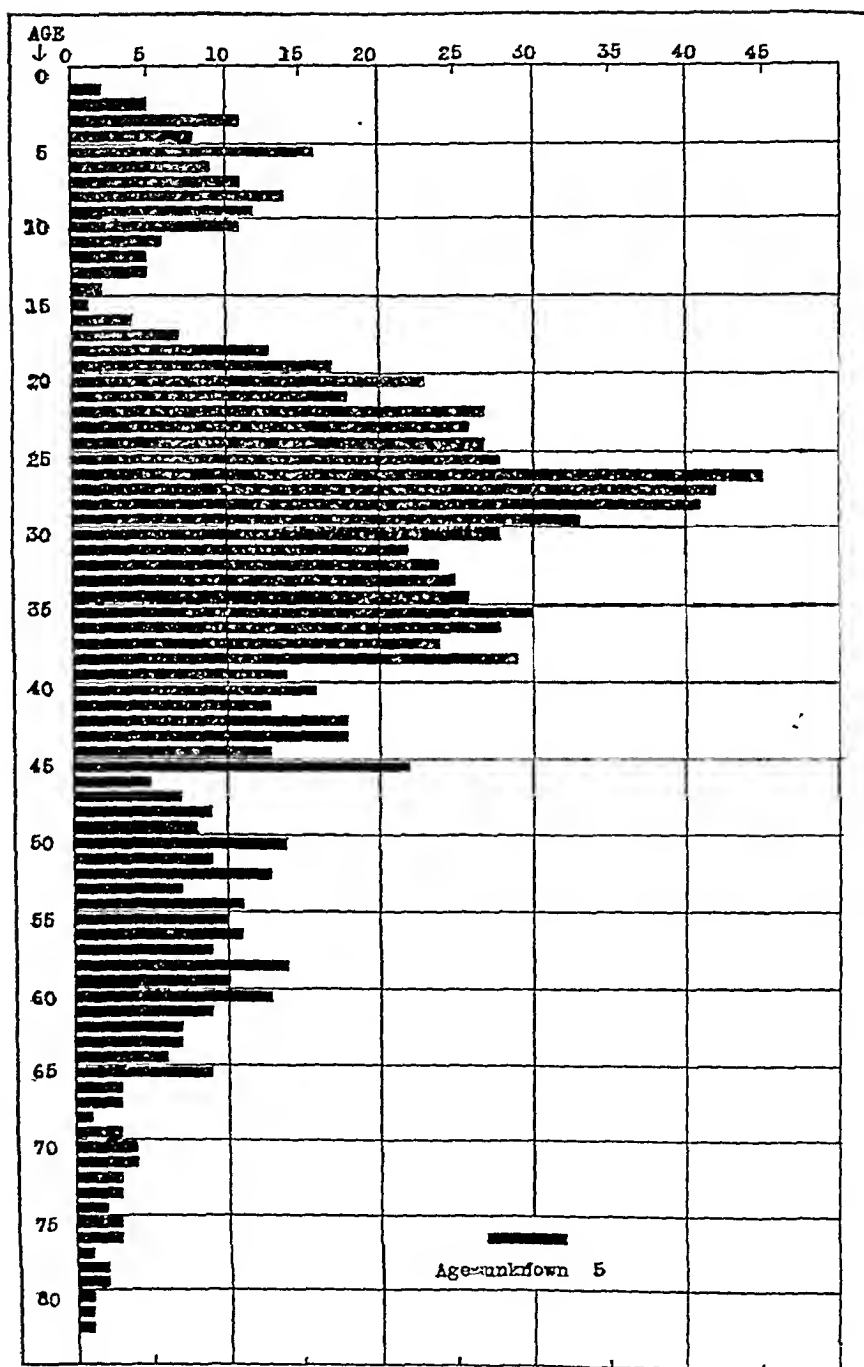


Fig. 6.—Total recorded recurrent attacks of pellagra distributed according to age of the patient at the beginning of the respective recurrent attack.

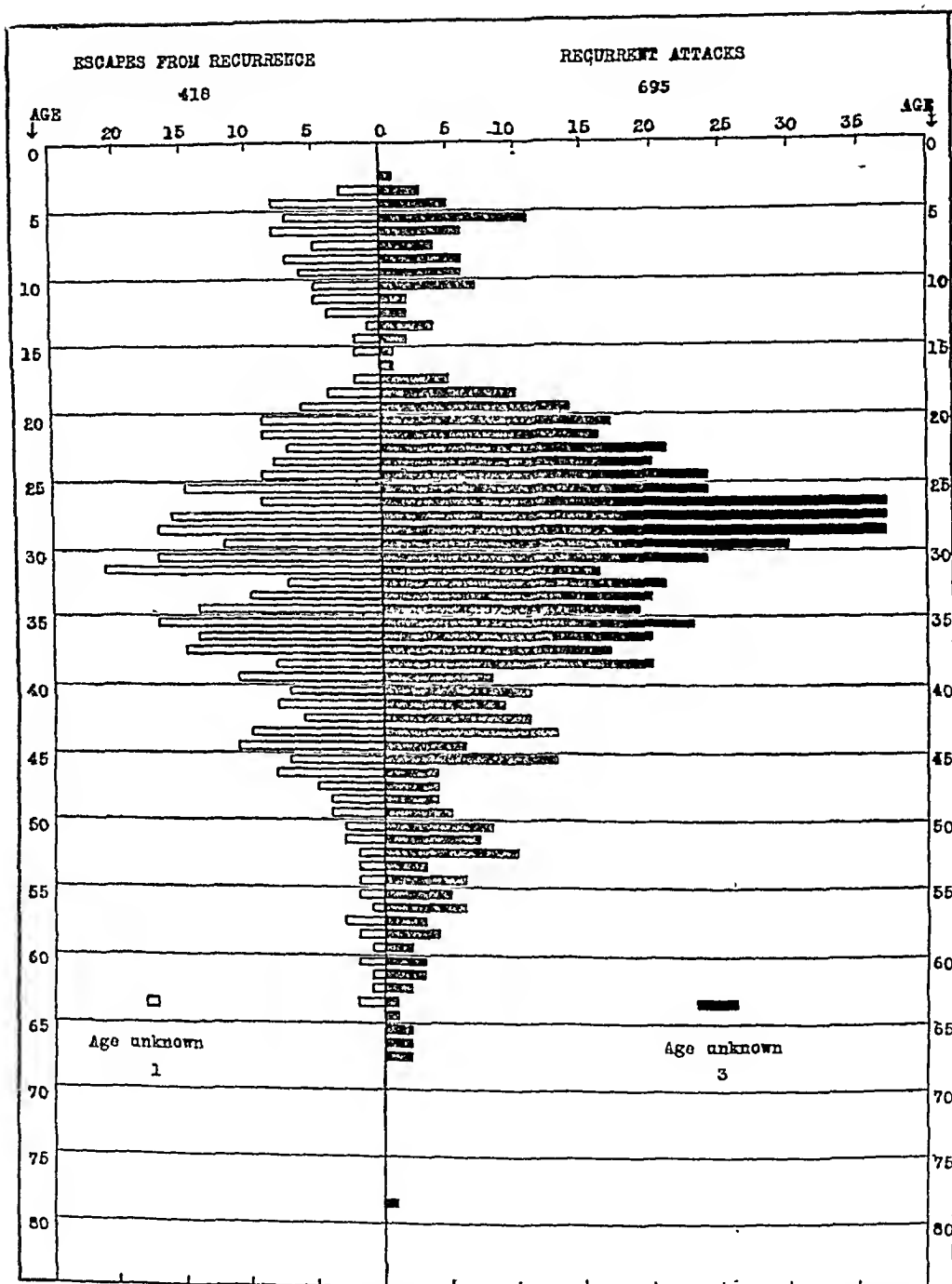


Fig. 7.—Instances of recurrent attack and of escape from recurrence of pellagra in white females, distributed according to age in the year of the respective observation.

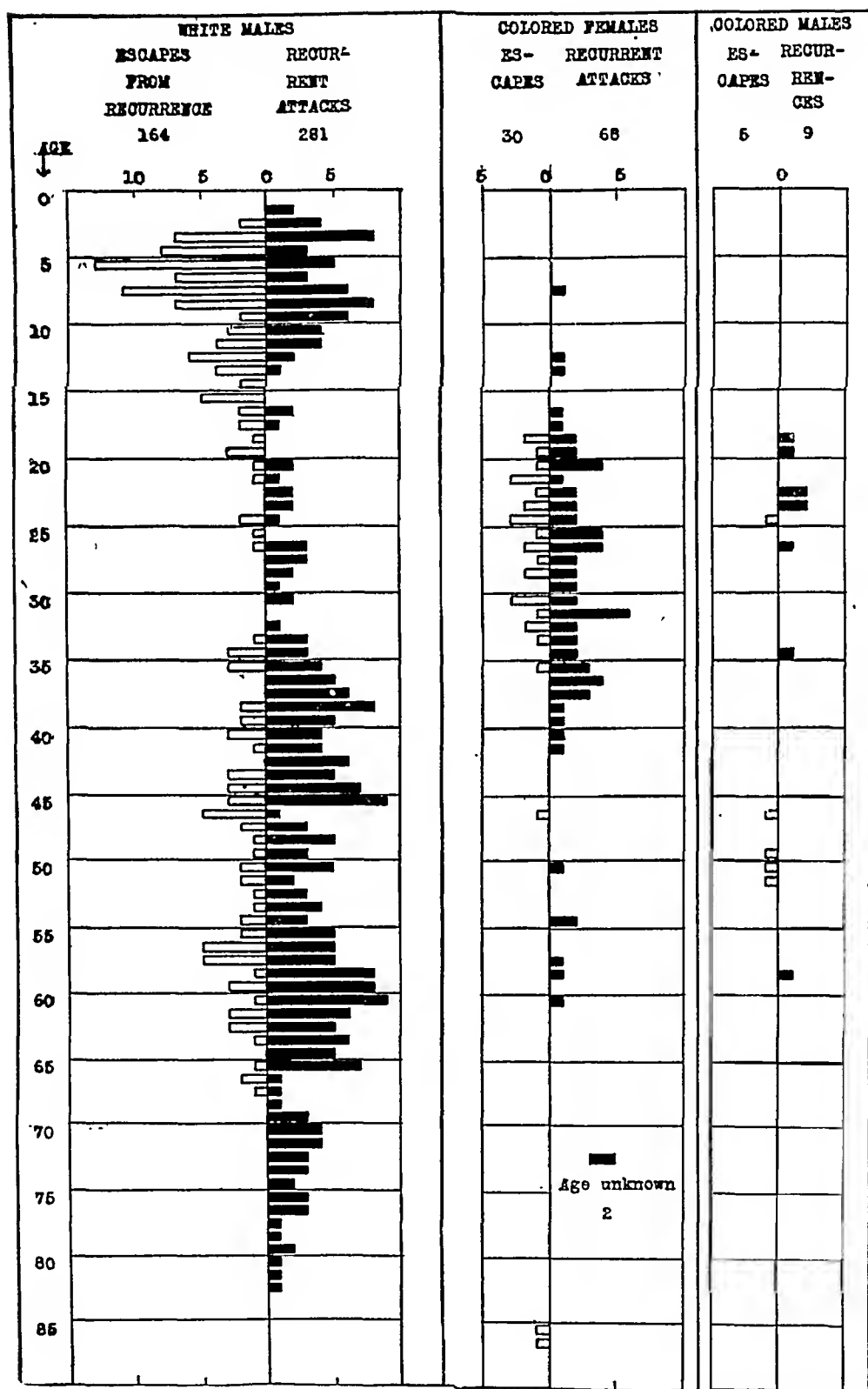


Fig. 8.—Instances of recurrent attack and of escape from recurrence of pellagra in white males, colored females and colored males, distributed according to race, sex and age in the year of the respective observation.

shown in Table 9 and presented graphically in Figures 6, 7 and 8. By comparing these figures with the distribution according to age at the onset of the initial attack shown in Figures 2, 3, 4 and 5 of a preceding paper² of this series, one will at once perceive important differences in the age distribution of recurrent and initial attacks of pellagra. The recurrences are relatively less numerous under the age of 10 years and the 15th, 16th and 17th years are especially conspicuous for the small number of recurrent attacks. The recurrences are relatively more numerous in adult life.

TABLE 10.—DISTRIBUTION OF RECURRENT ATTACKS OF PELLAGRA, ACCORDING TO AGE AT TIME OF RECURRENCE, SUMMARIZED BY FIVE-YEAR AGE PERIODS

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0 to 4.....	9	17	26	0	0	0	9	17	26
5 to 9.....	33	28	61	1	0	1	34	28	62
10 to 14.....	17	11	28	1	0	1	18	11	29
15 to 19.....	31	3	34	6	2	8	37	5	42
20 to 24.....	98	8	106	11	4	15	109	12	121
25 to 29.....	165	9	174	14	1	15	179	10	189
30 to 34.....	100	9	109	15	1	16	115	10	125
35 to 39.....	88	28	116	10	0	10	98	28	126
40 to 44.....	50	26	76	2	0	2	52	26	78
45 to 49.....	30	21	51	0	0	0	30	21	51
50 to 54.....	34	17	51	3	0	3	37	17	54
55 to 59.....	20	31	51	2	1	3	22	32	54
60 to 64.....	10	31	41	1	0	1	11	31	42
65 to 69.....	6	13	19	0	0	0	6	13	19
70 to 74.....	0	16	16	0	0	0	0	16	16
75 to 79.....	1	10	11	0	0	0	1	10	11
80 to 85.....	0	3	3	0	0	0	0	3	3
Age unknown.....	3	0	3	2	0	2	5	0	5
Total.....	695	281	976	63	9	77	763	290	1,053

The data of Table 9 are summarized according to age by 5-year periods in Table 10. The relatively small number of recurrences in pellagrins under the age of twenty years is quite evident. It is of interest to compare the number of observed recurrent attacks with the number of observed initial attacks in persons of the same age in this population. This comparison is shown in summarized form in Table

11. The number of recorded initial attacks was approximately equal to the number of recorded recurrent attacks in the whole group of white females, but under the age of 20 years recurrent attacks were relatively less frequent, constituting only 37 per cent. of the observed attacks in this age group. In women more than 20 years old the recurrent attacks were in the majority. The group of white males showed also a minority of recurrent attacks under 20 years of age, namely 21.1 per cent. of all observed in this age period. In older men, from age 20 to 44 years, the recurrences made up 47.1 per cent. of the observed attacks of pellagra, and after age 45 years they constituted 58.7 per

TABLE 11.—DISTRIBUTION OF INITIAL ATTACKS AND OF RECURRENT ATTACKS OF PELLAGRA OBSERVED IN SPARTANBURG COUNTY, ACCORDING TO RACE, SEX, AND AGE OF THE PATIENT AT ONSET OF THE RESPECTIVE ATTACK

Race and Sex	Age 0 to 19		Age 20 to 44		Age 45 and Over		Total	
	Initial	Recurrent	Initial	Recurrent	Initial	Recurrent	Initial†	Recurrent‡
White females....	153	90	447	501	97	101	710	695
White males.....	121	59	90	80	100	142	315	281
Colored females..	18	8	78	52	20	6	118	68
Colored males....	8	2	12	6	16	1	36	9
Total white.....	275*	149	537	581	197	243	1,026*	876
Total colored.....	26	10	90	58	36	7	154	77
Grand total.....	301*	159	627	639	233	250	1,180*	1,053*

* Including a white child, aged 2, of unknown sex.

† Including pellagrins of unknown age, as follows: thirteen white females, four white males, two colored females.

‡ Including pellagrins of unknown age as follows: three white females, two colored females

cent. of the recorded attacks of pellagra. In the negroes of both sexes the large majority of all attacks of pellagra observed were initial attacks. This relation depends chiefly on the high death rate in negroes in the initial attack for, as we have seen in Table 3, the instances in which negroes survived without recurrence were not very numerous.

THE RELATION OF ESCAPE FROM RECURRENCE TO RACE, SEX AND AGE IN THE YEAR OF OBSERVATION

Whenever a pellagrin survived a whole year without recurrence of the disease, this has been designated as a year without recurrence or as an escape from recurrence. In Table 12 these escapes from recurrence are tabulated according to the age of the patient in the year of

TABLE 12.—ESCAPES FROM RECURRENT ATTACK OF PELLAGRA, DISTRIBUTED
ACCORDING TO RACE, SEX AND AGE OF THE PATIENT
IN THE YEAR OF ESCAPE

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0.....	0	0	0	0	0	0	0	0	0
1.....	0	0	0	0	0	0	0	0	0
2.....	0	2	2	0	0	0	0	2	2
3.....	3	7	10	0	0	0	3	7	10
4.....	8	8	16	0	0	0	8	8	16
5.....	7	13	20	0	0	0	7	13	20
6.....	8	7	15	0	0	0	8	7	15
7.....	5	11	16	0	0	0	5	11	16
8.....	7	7	14	0	0	0	7	7	14
9.....	6	2	8	0	0	0	6	2	8
10.....	5	3	8	0	0	0	5	3	8
11.....	5	4	9	0	0	0	5	4	9
12.....	4	6	10	0	0	0	4	6	10
13.....	1	4	5	0	0	0	1	4	5
14.....	2	2	4	0	0	0	2	2	4
15.....	2	5	7	0	0	0	2	5	7
16.....	0	2	2	0	0	0	0	2	2
17.....	2	2	4	0	0	0	2	2	4
18.....	4	1	5	2	0	2	6	1	7
19.....	6	3	9	1	0	1	7	3	10
20.....	9	1	10	1	0	1	10	1	11
21.....	9	1	10	3	0	3	12	1	13
22.....	7	0	7	1	0	1	8	0	8
23.....	8	0	8	2	0	2	10	0	10
24.....	9	2	11	3	1	4	12	3	15
25.....	15	1	16	1	0	1	16	1	17
26.....	9	1	10	2	0	2	11	1	12
27.....	16	0	16	1	0	1	17	0	17
28.....	17	0	17	2	0	2	19	0	19
29.....	12	0	12	0	0	0	12	0	12
30.....	17	0	17	3	0	3	20	0	20
31.....	21	0	21	1	0	1	22	0	22
32.....	7	0	7	2	0	2	9	0	9
33.....	10	1	11	1	0	1	11	1	12
34.....	14	3	17	0	0	0	14	3	17
35.....	17	3	20	1	0	1	18	3	21
36.....	14	0	14	0	0	0	14	0	14
37.....	15	0	15	0	0	0	15	0	15
38.....	8	2	10	0	0	0	8	2	10
39.....	11	2	13	0	0	0	11	2	13
40.....	7	3	10	0	0	0	7	3	10
41.....	8	1	9	0	0	0	8	1	9
42.....	6	0	6	0	0	0	6	0	6
43.....	10	3	13	0	0	0	10	3	13
44.....	11	3	14	0	0	0	11	3	14
45.....	7	3	10	0	0	0	7	3	10
46.....	8	5	13	1	1	2	9	6	15
47.....	5	2	7	0	0	0	5	2	7
48.....	4	1	5	0	0	0	4	1	5
49.....	4	1	5	0	1	1	4	2	6
50.....	3	2	5	0	1	1	3	3	6
51.....	3	2	5	0	1	1	3	3	6
52.....	2	1	3	0	0	0	2	1	3
53.....	2	1	3	0	0	0	2	1	3
54.....	2	2	4	0	0	0	2	2	4
55.....	2	2	4	0	0	0	2	2	4
56.....	1	5	6	0	0	0	1	5	6
57.....	3	5	8	0	0	0	3	5	8
58.....	2	1	3	0	0	0	2	1	3
59.....	1	3	4	0	0	0	1	3	4

TABLE 12.—ESCAPES FROM RECURRENT ATTACK OF PELLAGRA, DISTRIBUTED ACCORDING TO RACE, SEX AND AGE OF THE PATIENT IN THE YEAR OF ESCAPE—(Continued)

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60.....	2	1	3	0	0	0	2	1	3
61.....	1	3	4	0	0	0	1	3	4
62.....	1	3	4	0	0	0	1	3	4
63.....	2	1	3	0	0	0	2	1	3
64.....	0	0	0	0	0	0	0	0	0
65.....	0	1	1	0	0	0	0	1	1
66.....	0	2	2	0	0	0	0	2	2
67.....	0	1	1	0	0	0	0	1	1
68.....	0	0	0	0	0	0	0	0	0
69.....	0	0	0	0	0	0	0	0	0
70.....	0	0	0	0	0	0	0	0	0
71.....	0	0	0	0	0	0	0	0	0
72.....	0	0	0	0	0	0	0	0	0
73.....	0	0	0	0	0	0	0	0	0
74.....	0	0	0	0	0	0	0	0	0
75.....	0	0	0	0	0	0	0	0	0
76.....	0	0	0	0	0	0	0	0	0
77.....	0	0	0	0	0	0	0	0	0
78.....	0	0	0	0	0	0	0	0	0
79.....	0	0	0	0	0	0	0	0	0
80.....	0	0	0	0	0	0	0	0	0
81.....	0	0	0	0	0	0	0	0	0
82.....	0	0	0	0	0	0	0	0	0
83.....	0	0	0	0	0	0	0	0	0
84.....	0	0	0	0	0	0	0	0	0
85.....	0	0	0	0	0	0	0	0	0
86.....	0	0	0	1	0	1	1	0	1
87.....	0	0	0	1	0	1	1	0	1
88.....	0	0	0	0	0	0	0	0	0
89.....	0	0	0	0	0	0	0	0	0
Total age known	417	164	581	30	5	35	447	169	616
Age unknown....	1	0	1	0	0	0	1	0	1
Total.....	418	164	582	30	5	35	448	169	617

escape. These are summarized in groups by 5-year age periods in Table 13.

By comparing the data of Tables 12 and 13 with the data of Tables 9 and 10, the significance of race, sex and age in relation to recurrence or nonrecurrence of pellagra in this population may be most clearly seen. This relationship is graphically presented in Figures 7 and 8. White girls under 10 years of age had forty-two recorded recurrences and forty-four recorded escapes from recurrence, the escapes being 51.2 per cent. of the sum. White boys under 10 years of age had forty-five recorded recurrences and fifty-seven recorded escapes from recurrence, the latter amounting to 55.9 per cent. of the sum. In the age period 10 to 14 years the white girls escaped recurrence in just 50 per cent. of the recorded observations, but the white boys escaped in 63.3 per cent. After the age of 15 the sex difference is much more manifest, the girls from 15 to 19 years escaping in 31.1 per cent. of the

observations, while the boys escaped in 81.2 per cent., in this age period. In the age period 20 to 44 years, the white women had 501 recorded recurrences and 287 escapes from recurrence, the escapes amounting to 36.4 per cent. of the sum. In the same age period, the white men had eighty recurrences and twenty-seven escapes, the latter being 25.2 per cent. of the sum. After the age of 45 years there were

TABLE 13.—ESCAPES FROM RECURRENT ATTACK OF PELLAGRA, DISTRIBUTED ACCORDING TO RACE, SEX AND AGE IN THE YEAR OF ESCAPE, SUMMARIZED BY FIVE-YEAR AGE PERIODS

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0 to 4.....	11	17	28	0	0	0	11	17	28
5 to 9.....	33	40	73	0	0	0	33	40	73
10 to 14.....	17	19	36	0	0	0	17	19	36
15 to 19.....	14	13	27	3	0	3	17	13	30
20 to 24.....	42	4	46	10	1	11	52	5	57
25 to 29.....	69	2	71	6	0	6	75	2	77
30 to 34.....	69	4	73	7	0	7	76	4	80
35 to 39.....	65	7	72	1	0	1	66	7	73
40 to 44.....	42	10	52	0	0	0	42	10	52
45 to 49.....	28	12	40	1	2	3	29	14	43
50 to 54.....	12	8	20	0	2	2	12	10	22
55 to 59.....	9	16	25	0	0	0	9	16	25
60 to 64.....	6	8	14	0	0	0	6	8	14
65 to 69.....	0	4	4	0	0	0	0	4	4
70 to 74.....	0	0	0	0	0	0	0	0	0
75 to 79.....	0	0	0	0	0	0	0	0	0
80 to 84.....	0	0	0	0	0	0	0	0	0
85 to 89.....	0	0	0	2	0	2	2	0	2
Age unknown.....	1	0	1	0	0	0	1	0	1
Total.....	418	164	582	30	5	35	448	169	617

101 recurrences and fifty-five escapes, or 35.3 per cent. of the sum, in white women, and in white men there were 142 recurrences and forty-eight escapes, the latter amounting to 25.3 per cent. of the sum.

In both sexes there is a very definite indication of increased resistance to recurrence at about the age of puberty. Thus in white girls aged 11 years there were two recurrences and five escapes out of seven observations, and at the age of 12 years there were two recurrences and four escapes out of six observations. This indication of increased resistance quickly disappears, and after the age of 16 the recurrences

predominate. In the white boys, on the other hand, the resistance to recurrence becomes evident at about the age of 12 years, and it disappears very much more gradually, the increased tendency to recur-

TABLE 14.—RELATIVE FREQUENCY OF RECURRENCE OF PELLAGRA IN THE DEFINITE RECORDS OF THE 814 PELLAGRINS WHO SURVIVED THE INITIAL ATTACK OF PELLAGRA PREVIOUS TO 1914, GROUPED ACCORDING TO RACE, SEX AND AGE IN THE YEAR OF THE RESPECTIVE OBSERVATION

Age in Year of Observation	Female			Male			Both Sexes		
	Total Definite Records	Recurrences		Total Definite Records	Recurrences		Total Definite Records	Recurrences	
		Number	Per Cent.		Number	Per Cent.		Number	Per Cent.
White pellagrins									
0 to 4.....	20	9	45	34	17	50	54	26	48.1
5 to 9.....	66	33	50	68	28	41.2	134	61	45.5
10 to 14.....	34	17	50	30	11	36.7	64	28	43.8
15 to 19.....	45	31	68.9	16	3	18.8	61	34	55.7
20 to 29.....	374	263	70.3	23	17	73.9	397	280	70.5
30 to 39.....	322	183	53.4	48	37	77.1	370	225	60.8
40 to 49.....	150	80	53.3	60	47	68.1	219	127	58
50 to 59.....	75	54	72	72	48	66.7	147	102	69.4
60 to 69.....	22	16	72.7	56	44	78.6	78	60	76.9
Over 70.....	1	1	100	29	29	100	30	30	100
Age unknown...	4	3	75	0	0	4	3	75
Total.....	1,113	695	62.4	445	281	63.1	1,558	976	62.6
Colored pellagrins									
0 to 4.....	0	0	0	0	0	0
5 to 9.....	1	1	100	0	0	1	1	100
10 to 14.....	1	1	100	0	0	1	1	100
15 to 19.....	9	6	66.7	2	2	100	11	8	72.7
20 to 29.....	41	25	61	6	5	83.3	47	30	63.8
30 to 39.....	33	25	75.8	1	1	100	34	26	76.5
40 to 49.....	3	2	66.7	2	0	0	5	2	40
50 to 59.....	5	5	100	3	1	33.3	8	6	75
60 to 69.....	1	1	100	0	0	1	1	100
Over 70.....	2	0	0	0	0	2	0	0
Age unknown...	2	2	100	0	0	2	2	100
Total.....	98	63	69.4	14	9	64.3	112	77	68.8
Total, both races	1,211	763	63	459	290	63.2	1,670	1,053	63.1

rence becoming apparent after the age of 25 years. In old age the men show less resistance to recurrence than do the women.

In Table 14 is presented a summary of the data relating to frequency of recurrence, the sum of observed recurrences and recorded

TABLE 15.—DEATHS IN RECURRENT ATTACK DISTRIBUTED ACCORDING TO RACE, SEX AND AGE AT ONSET OF THE FATAL RECURRENCE

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0.....	0	0	0	0	0	0	0	0	0
1.....	0	0	0	0	0	0	0	0	0
2.....	0	0	0	0	0	0	0	0	0
3.....	0	1	1	0	0	0	0	1	1
4.....	0	0	0	0	0	0	0	0	0
5.....	0	0	0	0	0	0	0	0	0
6.....	0	0	0	0	0	0	0	0	0
7.....	0	0	0	1	0	1	1	0	1
8.....	1	0	1	0	0	0	1	0	1
9.....	0	1	1	0	0	0	0	1	1
10.....	0	0	0	0	0	0	0	0	0
11.....	0	0	0	0	0	0	0	0	0
12.....	0	0	0	0	0	0	0	0	0
13.....	0	0	0	0	0	0	0	0	0
14.....	0	0	0	0	0	0	0	0	0
15.....	0	0	0	0	0	0	0	0	0
16.....	0	0	0	0	0	0	0	0	0
17.....	1	0	1	1	0	1	2	0	2
18.....	1	0	1	0	0	0	1	0	1
19.....	2	0	2	0	1	1	2	1	3
20.....	1	0	1	2	0	2	3	0	3
21.....	0	0	0	0	0	0	0	0	0
22.....	2	1	3	1	0	1	3	1	4
23.....	3	0	3	2	1	3	5	1	6
24.....	1	1	2	0	0	0	1	1	2
25.....	3	0	3	2	0	2	5	0	5
26.....	4	0	4	0	0	0	4	0	4
27.....	3	0	3	0	0	0	3	0	3
28.....	2	0	2	1	0	1	3	0	3
29.....	2	0	2	0	0	0	2	0	2
30.....	2	1	3	0	0	0	2	1	3
31.....	4	0	4	1	0	1	5	0	5
32.....	0	0	0	0	0	0	0	0	0
33.....	2	0	2	0	0	0	2	0	2
34.....	3	2	5	0	1	1	3	3	6
35.....	3	0	3	0	0	0	3	0	3
36.....	4	0	4	0	0	0	4	0	4
37.....	1	1	2	1	0	1	2	1	3
38.....	0	1	1	1	0	1	1	1	2
39.....	0	0	0	0	0	0	0	0	0
40.....	2	0	2	1	0	1	3	0	3
41.....	0	1	1	0	0	0	0	1	1
42.....	0	0	0	0	0	0	0	0	0
43.....	1	2	3	0	0	0	1	2	3
44.....	0	2	2	0	0	0	0	2	2
45.....	5	3	8	0	0	0	5	3	8
46.....	0	1	1	0	0	0	0	1	1
47.....	0	0	0	0	0	0	0	0	0
48.....	0	3	3	0	0	0	0	3	3
49.....	0	1	1	0	0	0	0	1	1
50.....	2	1	3	1	0	1	3	1	4
51.....	0	1	1	0	0	0	0	1	1
52.....	2	1	3	0	0	0	2	1	3
53.....	1	1	2	0	0	0	1	1	2
54.....	2	0	2	1	0	1	3	0	3
55.....	0	1	1	0	0	0	0	1	1
56.....	1	1	2	0	0	0	1	1	2
57.....	0	0	0	0	0	0	0	0	0
58.....	1	0	1	1	1	2	2	1	3
59.....	0	2	2	0	0	0	0	2	2

TABLE 15.—DEATHS IN RECURRENT ATTACK DISTRIBUTED ACCORDING TO RACE, SEX AND AGE AT ONSET OF THE FATAL RECURRENCE—(Continued)

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
60.....	1	2	3	1	0	1	2	2	4
61.....	0	1	1	0	0	0	0	1	1
62.....	0	2	2	0	0	0	0	2	2
63.....	0	1	1	0	0	0	0	1	1
64.....	0	1	1	0	0	0	0	1	1
65.....	1	2	3	0	0	0	1	2	3
66.....	0	0	0	0	0	0	0	0	0
67.....	0	0	0	0	0	0	0	0	0
68.....	0	0	0	0	0	0	0	0	0
69.....	0	0	0	0	0	0	0	0	0
70.....	0	0	0	0	0	0	0	0	0
71.....	0	0	0	0	0	0	0	0	0
72.....	0	0	0	0	0	0	0	0	0
73.....	0	0	0	0	0	0	0	0	0
74.....	0	0	0	0	0	0	0	0	0
75.....	0	0	0	0	0	0	0	0	0
76.....	0	2	2	0	0	0	0	2	2
77.....	0	0	0	0	0	0	0	0	0
78.....	0	0	0	0	0	0	0	0	0
79.....	0	1	1	0	0	0	0	1	1
80.....	0	0	0	0	0	0	0	0	0
81.....	0	0	0	0	0	0	0	0	0
82.....	0	0	0	0	0	0	0	0	0
83.....	0	0	0	0	0	0	0	0	0
84.....	0	0	0	0	0	0	0	0	0
Total age known	64	42	106	18	4	22	82	46	128
Age unknown....	1	0	1	1	0	1	2	0	2
Total.....	65	42	107	19	4	23	84	46	130

TABLE 16.—DEATHS IN RECURRENT ATTACK, DISTRIBUTED ACCORDING TO RACE, SEX AND AGE AT ONSET OF THE FATAL RECURRENCE, SUMMARIZED BY TEN-YEAR AGE PERIODS

Age, Years	White			Colored			Both Races		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
0 to 9.....	1	2	3	1	0	1	2	2	4
10 to 19.....	4	0	4	1	1	2	5	1	6
20 to 29.....	21	2	23	8	1	9	29	3	32
30 to 39.....	19	5	24	3	1	4	22	6	28
40 to 49.....	8	13	21	1	0	1	9	13	22
50 to 59.....	9	8	17	3	1	4	12	9	21
60 to 69.....	2	9	11	1	0	1	3	9	12
70 to 79.....	0	3	3	0	0	0	0	3	3
Age unknown.....	1	0	1	1	0	1	2	0	2
Total.....	65	42	107	19	4	23	84	46	130

escapes from recurrence for each age period being taken as the total definite records and the ratio of the observed recurrences to this being expressed as per cent. of the total observations. Thus, in white girls in the age period 0 to 4 years there were nine recurrences and eleven

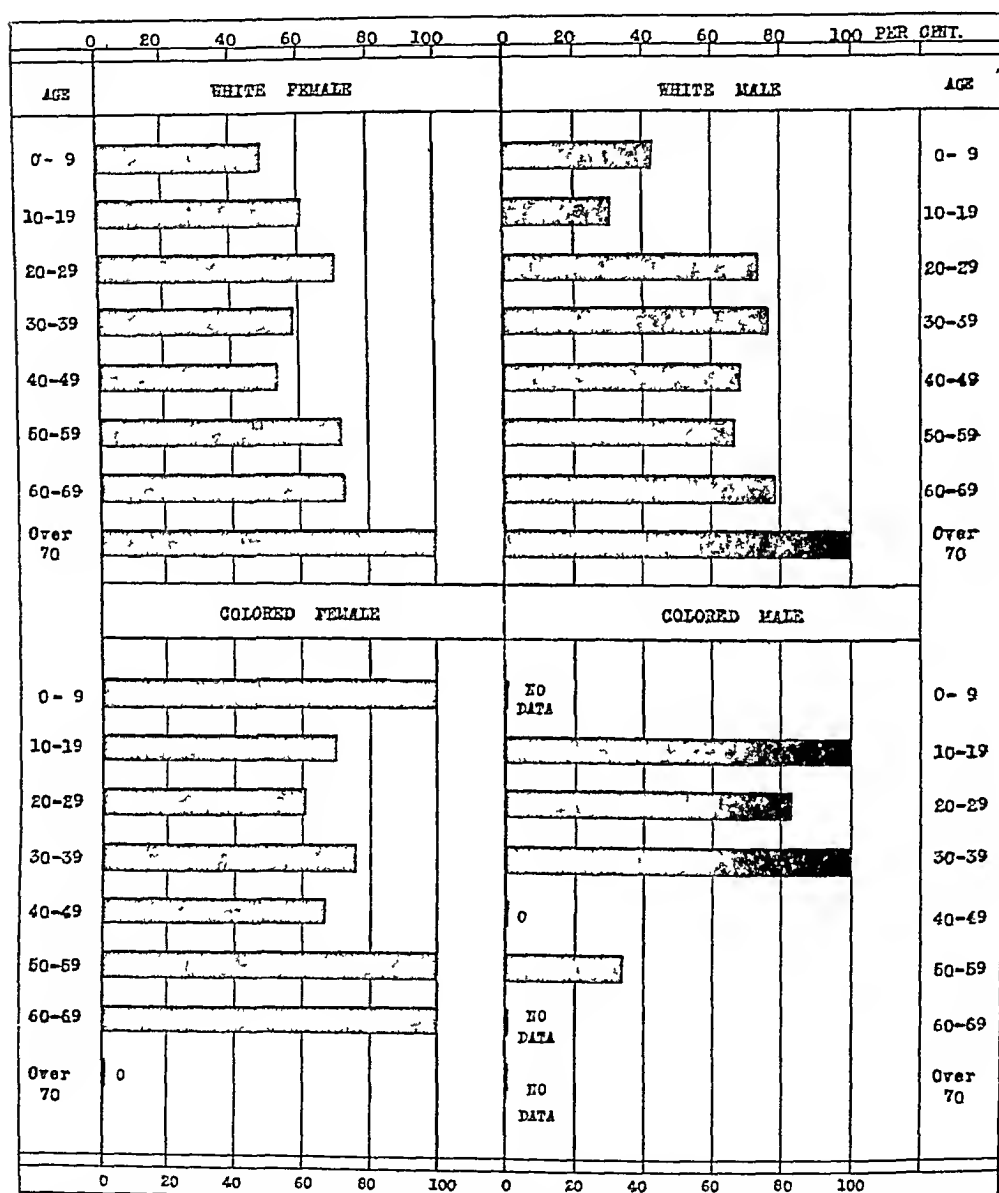


Fig. 9.—Relative frequency of recurrence in each age period for each sex and race, expressed in percentage of the total instances of definite record for the respective age group, according to age at the time of observation.

escapes from recurrence, the recurrences amounting to 45 per cent. of the sum. The relative frequency of recurrence for each decade of life is shown graphically in Figure 9, the length of each bar representing the percentage of recurrences in the total definite records for the respective age group. In the negroes the number of observations for

most of the age periods is very small, so that the percentages have little significance. For the white race, however, they are more significant. The greater frequency of recurrence in older men, the marked tendency for boys from 10 to 19 years of age to escape recurrence and the relatively low recurrence rate in children under 10 years are clearly evident. The women seem definitely more subject to recurrence in the third decade of life than in the fourth or fifth decades and the large number of observations on which these percentages are based in these age periods gives the observed difference considerable significance. Probably this difference may be correlated with the greater frequency of childbirth in the third decade of the life of these women. After the age of 50 the recurrence rate is again relatively high.

THE RELATION BETWEEN DEATH RATE AND AGE AT THE TIME OF RECURRENT ATTACK

The 130 deaths in recurrent attack of pellagra are shown in Table 15, distributed according to race, sex and age at the onset of the fatal attack. In Table 16 the deaths are summarized by 10 year age periods. The great majority of the deaths in recurrence evidently occurred in patients more than 20 years old.

In Table 17 are presented the death rates in recorded recurrent attacks of pellagra for each race and sex by decades of life, the data being taken from Tables 10 and 16. For the white race, as a whole, the death rate in recurrence mounts progressively from 3.4 per cent. in the first decade of life to 18.3 per cent. in the seventh decade. This tendency is also evident in all the race-sex groups, although there are some irregular variations. Thus the white women show their highest death rate, 16.7 per cent., in the sixth decade and the white men show the greatest death rate in the fifth, namely, 27.7 per cent. There were fourteen recurrences in white boys in the second decade of life, without any deaths. The children under 10 years of age are also conspicuous for their low death rate in recurrent attack. The data of Table 17 are presented graphically in Figure 10.

It is probably too early to form a reliable judgment concerning the importance of pellagra in children. The data accumulated during the few years of our study show very clearly a high incidence of pellagra in children residing in the endemic foci of the disease. The vast majority of them survived the initial attack. The tendency for recurrence to appear in the immediately following years is less marked than in adults and the death rate in recurrence, when it does appear, is again very low. At about the age of puberty the tendency to escape recurrence is evidently augmented. The prognosis is therefore comparatively very good in pellagrous children. Whether or not these

The following is a summary of the results of the study conducted by the American Medical Association in 1934. The study was designed to determine the effect of the new medical education requirements on the quality of medical education in the United States. The results of the study are as follows:

The study found that the new medical education requirements have had a significant effect on the quality of medical education in the United States. The results of the study are as follows:

Year	1934		1935		1936		1937		1938		1939		1940		1941		1942		1943		1944		1945		1946		1947		1948		1949		1950		1951		1952		1953		1954		1955		1956		1957		1958		1959		1960		1961		1962		1963		1964		1965		1966		1967		1968		1969		1970		1971		1972		1973		1974		1975		1976		1977		1978		1979		1980		1981		1982		1983		1984		1985		1986		1987		1988		1989		1990		1991		1992		1993		1994		1995		1996		1997		1998		1999		2000		2001		2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012		2013		2014		2015		2016		2017		2018		2019		2020		2021		2022		2023		2024		2025		2026		2027		2028		2029		2030		2031		2032		2033		2034		2035		2036		2037		2038		2039		2040		2041		2042		2043		2044		2045		2046		2047		2048		2049		2050		2051		2052		2053		2054		2055		2056		2057		2058		2059		2060		2061		2062		2063		2064		2065		2066		2067		2068		2069		2070		2071		2072		2073		2074		2075		2076		2077		2078		2079		2080		2081		2082		2083		2084		2085		2086		2087		2088		2089		2090		2091		2092		2093		2094		2095		2096		2097		2098		2099		2100		2101		2102		2103		2104		2105		2106		2107		2108		2109		2110		2111		2112		2113		2114		2115		2116		2117		2118		2119		2120		2121		2122		2123		2124		2125		2126		2127		2128		2129		2130		2131		2132		2133		2134		2135		2136		2137		2138		2139		2140		2141		2142		2143		2144		2145		2146		2147		2148		2149		2150		2151		2152		2153		2154		2155		2156		2157		2158		2159		2160		2161		2162		2163		2164		2165		2166		2167		2168		2169		2170		2171		2172		2173		2174		2175		2176		2177		2178		2179		2180		2181		2182		2183		2184		2185		2186		2187		2188		2189		2190		2191		2192		2193		2194		2195		2196		2197		2198		2199		2200		2201		2202		2203		2204		2205		2206		2207		2208		2209		2210		2211		2212		2213		2214		2215		2216		2217		2218		2219		2220		2221		2222		2223		2224		2225		2226		2227		2228		2229		2230		2231		2232		2233		2234		2235		2236		2237		2238		2239		2240		2241		2242		2243		2244		2245		2246		2247		2248		2249		2250		2251		2252		2253		2254		2255		2256		2257		2258		2259		2260		2261		2262		2263		2264		2265		2266		2267		2268		2269		2270		2271		2272		2273		2274		2275		2276		2277		2278		2279		2280		2281		2282		2283		2284		2285		2286		2287		2288		2289		2290		2291		2292		2293		2294		2295		2296		2297		2298		2299		2300		2301		2302		2303		2304		2305		2306		2307		2308		2309		2310		2311		2312		2313		2314		2315		2316		2317		2318		2319		2320		2321		2322		2323		2324		2325		2326		2327		2328		2329		2330		2331		2332		2333		2334		2335		2336		2337		2338		2339		2340		2341		2342		2343		2344		2345		2346		2347		2348		2349		2350		2351		2352		2353		2354		2355		2356		2357		2358		2359		2360		2361		2362		2363		2364		2365		2366		2367		2368		2369		2370		2371		2372		2373		2374		2375		2376		2377		2378		2379		2380		2381		2382		2383		2384		2385		2386		2387		2388		2389		2390		2391		2392		2393		2394		2395		2396		2397		2398		2399		2400		2401		2402		2403		2404		2405		2406		2407		2408		2409		2410		2411		2412		2413		2414		2415		2416		2417		2418		2419		2420		2421		2422		2423		2424		2425		2426		2427		2428		2429		2430		2431		2432		2433		2434		2435		2436		2437		2438		2439		2440		2441		2442		2443		2444		2445		2446		2447		2448		2449		2450		2451		2452		2453		2454		2455		2456		2457		2458		2459		2460		2461		2462		2463		2464		2465		2466		2467		2468		2469		2470		2471		2472		2473		2474		2475		2476		2477		2478		2479		2480		2481		2482		2483		2484		2485		2486		2487		2488		2489		2490		2491		2492		2493		2494		2495		2496		2497		2498		2499		2500		2501		2502		2503		2504		2505		2506		2507		2508		2509		2510		2511		2512		2513		2514		2515		2516		2517		2518		2519		2520		2521		2522		2523		2524		2525		2526		2527		2528		2529		2530		2531		2532		2533		2534		2535		2536		2537		2538		2539		2540		2541		2542		2543		2544		2545		2546		2547		2548		2549		2550		2551		2552		2553		2554		2555		2556		2557		2558		2559		2560		2561		2562		2563		2564		2565		2566		2567		2568		2569		2570		2571		2572		2573		2574		2575		2576		2577		2578		2579		2580		2581		2582		2583		2584		2585		2586		2587		2588		2589		2590		2591		2592		2593		2594		2595		2596		2597		2598		2599		2600		2601		2602		2603		2604		2605		2606		2607		2608		2609		2610		2611		2612		2613		2614		2615		2616		2617		2618		2619		2620		2621		2622		2623		2624		2625		2626		2627		2628		2629		2630		2631		2632		2633		2634		2635		2636		2637		2638		2639		2640		2641		2642		2643		2644		2645		2646		2647		2648		2649		2650		2651		2652		2653		2654		2655		2656		2657		2658		2659		2660		2661		2662		2663		2664		2665		2666		2667		2668		2669		2670		2671		2672		2673		2674		2675		2676		2677		2678		2679		2680		2681		2682		2683		2684		2685		2686		2687		2688		2689		2690		2691		2692		2693		2694		2695		2696		2697		2698		2699		2700		2701		2702		2703		2704		2705		2706		2707		2708		2709		2710		2711		2712		2713		2714		2715		2716		2717		2718		2719		2720		2721		2722		2723		2724		2725		2726		2727		2728		2729		2730		2731		2732		2733		2734		2735		2736		2737		2738		2739		2740		2741		2742		2743		2744		2745		2746		2747		2748		2749		2750		2751		2752		2753		2754		2755		2756		2757		2758		2759		2760		2761		2762		2763		2764		2765		276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pellagra. The occasional cases of pellagra appearing in persons who have resided at a distance from the foci of the disease for many years may be instances of this kind.

RELATION OF RECURRENDE TO TREATMENT

The treatment of pellagra presents two phases for discussion, (1) the management of the case during the attack of the disease, and (2)

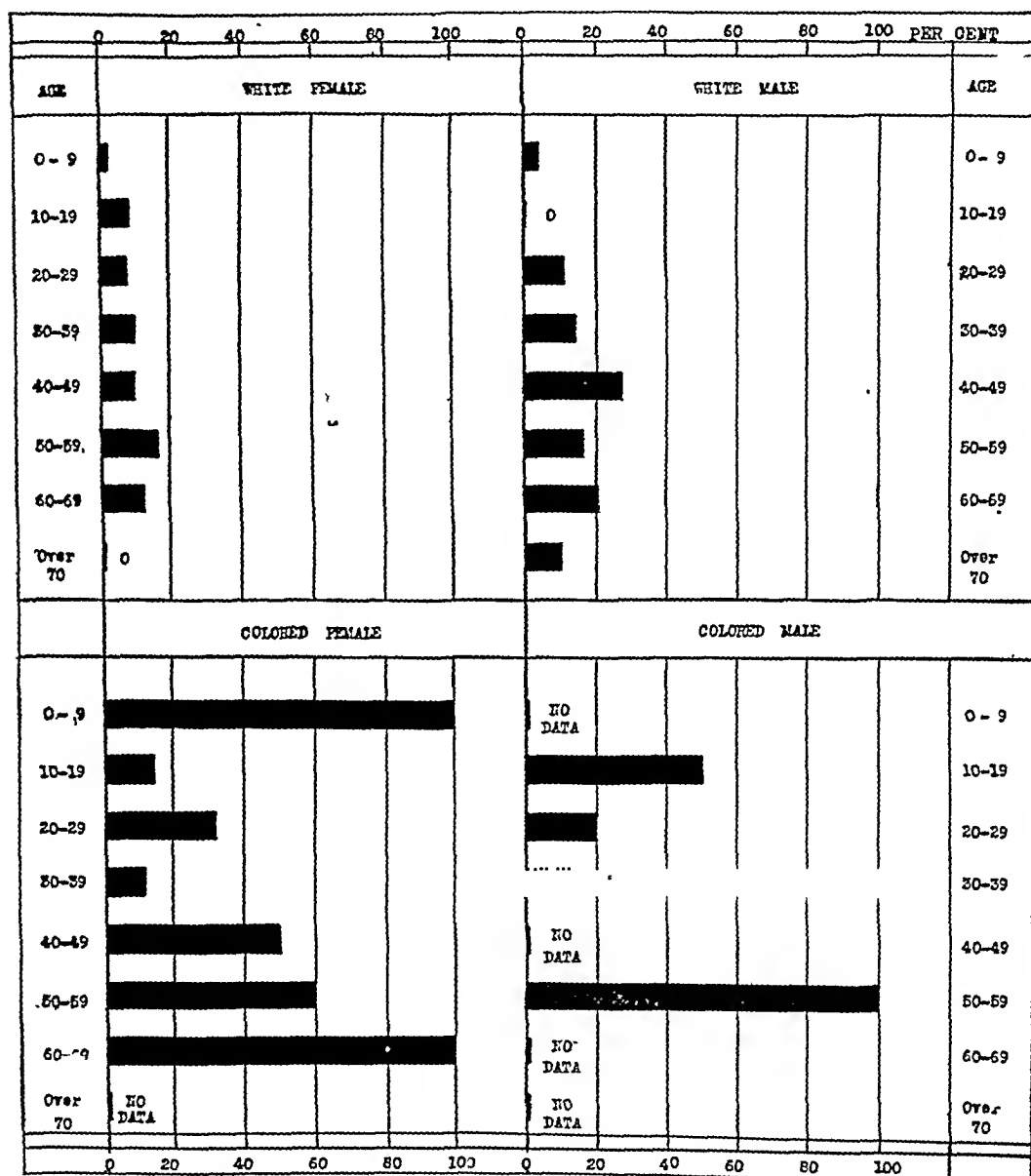


Fig. 10.—Death rate in recurrent attack, expressed in percentage, for each race, sex and 10-year age group, according to age at the time of the recurrent attack.

the management of the patient after recovery from the attack. We hope to present in detail in another paper the records of several cases observed in the hospital during the attack. In the present section we shall consider the record over a period of years of some of the pella-

grins in our series, who have received definite treatment for pellagra at one time or another. The vast majority of the cases in the series have not been given any treatment directed against the disease and this statement is applicable to nearly all of the children. There can be no question, therefore, of the fact that the acute attack of pellagra tends, in the vast majority of patients, to spontaneous recovery. By selecting patients not seriously ill and beginning treatment in the late summer, any conservative physician should be able, with the cooperation of an efficient nurse, to obtain a very large proportion of recoveries. As a rule, those patients who receive treatment receive it during the attack and relatively few continue to be treated during the remainder of the year. Certainly every pellagrin should, if possible, be kept under close medical supervision until at least one summer has passed without any symptoms of the disease.

The first group we wish to consider consists of the fourteen pellagrins who were transported from South Carolina to the New York Post-Graduate Hospital by us in the summer of 1912. These cases were selected for severity in order to provide subjects for observation and study during the acute attack of pellagra and for postmortem examination in the event of death. The details of the treatment and the clinical observations on these patients will not be gone into here. It is sufficient to say that they received a diet of milk and vegetables⁴ and no specific drug treatment during the acute attack. In all cases the manifestations of pellagra disappeared and the patients returned to their homes after intervals varying from two weeks to three months. During their stay in the hospital these patients had opportunity to learn by precept and example many things relating to personal hygiene and dietetics. All were white people and all but one of them were women. The summarized record of each of the fourteen patients will be briefly stated.

1. Pellagrin 2131, man, a resident of South Carolina outside of Spartanburg County, was born Nov. 26, 1851, in Union County, S. C. He was a farmer, owning land valued at \$2,000. His first attack of pellagra occurred in 1911, the diagnostic erythema appearing in September of that year. He did not regain his strength during the winter. The eruption on the hands recurred in a mild form several times from September, 1911, to June, 1912. He was admitted to the Post-Graduate Hospital on June 4, 1912, and discharged on June 25, 1912, when he returned to his home. During his stay in the hospital the eruption disappeared from his hands and there was a distinct gain in physical and mental vigor, but a net loss in weight from 145 to 144 pounds. His subsequent history is somewhat uncertain. In 1913 there was no definite eruption, but the weakness still persisted. In August, 1913, he weighed 161½ pounds. A letter from him in April, 1914, states that he was then still weak and nervous, with subjective burning on his hands, but no eruption as yet.

4. The daily menu of these patients has been published by Myers and Fine, *Am. Jour. Med. Sc.*, 1913, cxlv, 705; *First Progress Report*, 1914, 111.

2. Pellagrin 1, girl, aged 17 in 1912, had her first attack of pellagra in February, 1911. The erythema recurred in May, 1912. She was brought to New York and admitted to the Post-Graduate Hospital on June 4, 1912. Her symptoms improved almost at once, and she was sent home without recognizable manifestations of pellagra on July 11, 1912. During the latter part of her stay in the hospital she ate maize foods three times a day. Her health remained good during the remainder of 1912, but she suffered recurrence of pellagra in February, 1913, and again in February, 1914.

3. Pellagrin 2, woman, aged 37 in 1912, married and the mother of five children, was a neurotic woman and had been confined in the Columbia state hospital for the insane in the fall and winter of 1912. Her psychosis was of the manic-depressive type. After returning home her initial pellagrous erythema appeared on May 26, 1912. She was brought to New York and admitted to the Post-Graduate Hospital on June 4, 1912. Her admission weight was 94½ pounds. The attack was a severe one and she lay in a typhoid state for several days, her weight diminishing to 85½ pounds. During convalescence the symptoms of mania reappeared and it was deemed advisable to remove her to a special hospital for nervous diseases. After the manifestations of pellagra had disappeared, she was taken home on the earnest demand of her husband on August 15, 1912, but her nervous state was such that he soon had her committed again to the state hospital, where she remained for some months. She gained very rapidly in weight, weighing 114 pounds on Oct. 3, 1912, and her mental disturbance gradually disappeared, so that she was sent home again during the winter. The family sold their farm for about \$1,500 and moved to North Carolina, where the patient died early in the spring of 1913 without evident recurrence of pellagra.

4. Pellagrin 9, woman, aged 32 in 1912, suffered her initial attack of pellagra in July, 1910. She escaped recurrence in 1911, but the disease reappeared about June 1, 1912. She was admitted to the Post-Graduate Hospital on July 2, 1912, and discharged free from manifestations of pellagra on July 27, 1912. She returned home and died in April, 1913, without recurrence of pellagra.

5. Pellagrin 12, woman, aged 40 in 1912, suffered her first attack of pellagra in July, 1911, with recurrence in April, 1912. She was admitted to the Post-Graduate Hospital on July 2, 1912, and discharged free from manifestations of pellagra on July 27, 1912. She returned home and remained well during the remainder of 1912. In May, 1913, the disease recurred. During this attack and for some months subsequent to it she received repeated subcutaneous injections of sodium cacodylate. There was a recurrence again in March, 1914, from which she recovered in July, 1914. This patient was a woman of intelligence and refinement and in good financial circumstances.

6. Pellagrin 68, woman, aged 36 in 1912, had her initial attack of pellagra in May, 1911, with recurrence early in July, 1912. She was admitted to the Post-Graduate Hospital on July 16, 1912, and sent home free from recognizable manifestations of pellagra on Aug. 14, 1912. She gained 14 pounds in weight during her stay in the hospital. In 1913 there were repeated mild recurrences of the eruption and she went to Savannah, Ga., where she was treated in the hospital of the U. S. Public Health Service from Feb. 27 to April 1, 1914. In June, 1914, she again suffered a severe recurrence.

7. Pellagrin 113, woman, aged 20 in 1912, suffered her initial attack of pellagra in July, 1912. She was admitted to the Post-Graduate Hospital on July 30, 1912, and discharged free from recognizable manifestations of pellagra on Aug. 27, 1912. The eruption in her case was very extensive, involving lower as well as upper limbs and also extending as a broad belt around the waist. She returned home and remained free from recurrence in 1913 and 1914.

8. Pellagrin 114, woman, aged 18 in 1912, a social intimate of the preceding patient, suffered her initial attack of pellagra also in July, 1912. She was admitted to the Post-Graduate Hospital on July 30, 1912, and discharged free

from recognizable manifestations of pellagra on Aug. 14, 1912. She returned home and remained well during the remainder of the year. In May, 1913, the eruption reappeared and the attack progressed favorably, clearing up early in July. Early in September, 1913, there was another recurrence, which cleared up after about six weeks, but left her weak and emaciated. In January, 1914, the erythema reappeared for about three weeks and left her with well-marked mental derangement. Her family kept her at home, however, and the mental disturbance gradually passed away. About May 1 the erythema reappeared with distressing diarrhea, weakness and emaciation. At this time she was seen by us and, although in distress, she was very clear in her mind and was by no means discouraged in spirit. The symptoms gradually disappeared and in August she appeared well again and was actively at work.

9. Pellagrin 21, woman, aged 28 in 1912, suffered her first attack of pellagra in May, 1911, with recurrence in May, 1912. She was admitted to the Post-Graduate Hospital on Aug. 11, 1912, and discharged free from recognizable manifestations of pellagra on Sept. 6, 1912. Her condition was complicated by a large cystic ovarian tumor, which had been repeatedly tapped and was tapped once during her stay in the hospital. She was advised to have a radical operation late in the fall after her attack of pellagra had subsided, but she was unwilling to undergo the operation. She was sent home, free from recognizable manifestations of pellagra, on Sept 6, 1912. There was a severe recurrence, beginning in April, 1913, and persisting until the middle of July. She died March 4, 1914, without recurrence of pellagra in that year.

10. Pellagrin 115, woman, aged 28 in 1912, suffered her first attack of pellagra in June, 1909, with recurrences in June, 1910, June, 1911, and May, 1912. She was admitted to the Post-Graduate Hospital on Aug. 11, 1912, and sent home free from recognizable manifestations of pellagra on Aug. 27, 1912, having gained 6 pounds in weight. She suffered recurrence in May or June, 1913, and was sent to Savannah, where she was treated in the hospital of the U. S. Public Health Service during the summer. In 1914 she had a severe recurrence beginning early in March and leading to severe mental disturbance and death in the state hospital for the insane in November, 1914.

11. Pellagrin 158, woman, aged 33 in 1912, suffered her first attack of pellagra in July, 1912. She was admitted to the Post-Graduate Hospital on Aug. 17, 1912, discharged on Sept. 26, 1912, and was sent home free from recognizable manifestations of pellagra. There were clear physical signs of active tuberculosis throughout the upper lobe of the right lung and numerous acid-proof bacilli in her sputum. During her stay in the hospital she gained 33 pounds in weight, from 90 pounds on admission to 123 pounds on the day of discharge. After returning home she continued her diet of milk and eggs and has had an outdoor sleeping porch constructed and has slept there regularly. In 1913 she remained well enough to work in the mill, but there was a definite recurrence of the pellagrous erythema in June. She was seen by us on March 26, 1914, at which time there was no evidence of pellagra. The directions in regard to sleeping and diet seemed to be well followed. Unfortunately, it was necessary for her to work all the time. Her weight was then 105 pounds and her voice was somewhat husky. On June 2, 1914, she had a recurrence of the pellagrous erythema accompanied by extreme weakness.

This patient is of some interest because of the recurrence of the pellagrous erythema while she was on a rich diet for the treatment of tuberculosis. Such cases are by no means uncommon in institutions where pellagra and tuberculosis exist together. For example, several cases of pellagra appeared in the cottages and tent colonies of tuberculous patients at the Peoria State Hospital during 1909 and 1910. The existence of such cases seems to have been overlooked by those who would see in the lack of food the essential and sole cause of pellagra.

12. Pellagrin 166, woman, aged 35 in 1912, suffered her first attack of pellagra early in July, 1912. She was admitted to the Post-Graduate Hospital on Aug. 23, 1912, and discharged free from recognizable manifestations of pellagra on Sept. 9, 1912. She returned home and remained free from recurrence of the disease in 1913 and 1914. This patient was an intelligent woman in good financial circumstances and seems to have continued at home the hygienic-dietetic measures which she learned in the hospital.

13. Pellagrin 206, woman, aged 48 in 1912, suffered her initial attack of pellagra in April, 1911, with recurrence in April, 1912. The latter attack was prolonged and an active eruption was still present when she was admitted to the Post-Graduate Hospital on Sept. 5, 1912. She was discharged free from recognizable manifestations of pellagra on Sept. 26, 1912. She suffered a recurrence in September, 1913, and again in April, 1914.

14. Pellagrin 170, woman, aged 34 in 1912, suffered her initial attack of pellagra in June, 1911. She continued at work until late in the summer, when she was confined to bed for several weeks. The attack left her somewhat demented and she was an inmate of the state hospital at Columbia, S. C., from Dec. 12, 1911, to Feb. 7, 1912. About May 15, 1912, there was a recurrence of pellagra. She was selected as an almost hopeless case and sent to New York for observation, being admitted to the Post-Graduate Hospital on Sept. 5, 1912. She then weighed 67 pounds, was extremely weak, rational only at intervals, with eruption involving hands, forearms, arms, shoulders, neck and face. She had an uncontrollable diarrhea and loss of control of bladder sphincter as well. On September 28 she was transferred to the general ward for convalescence, her eruption having disappeared, although the diarrhea and dementia still persisted. Her weight had increased to 75 pounds. On October 3 daily injections of 3 grains of sodium cacodylate were begun and these were daily continued during the remainder of her stay in the hospital. She was sent home on Nov. 18, 1912, weighing 95 pounds and clear in her mind, although somewhat sluggish in her mental activity. She remained free from recurrence in 1913 and 1914, working steadily in the cotton mill. She was seen in May, 1914, and again in September, 1914, and on both occasions her mental activity appeared quite normal.

The ultimate results after two years in this series of fourteen cases lend very little support to the idea that a short period of residence in a hospital can ordinarily be expected to bring about a permanent recovery from pellagra. Only three of these patients remained free from symptoms during the following two years. One of these, Pellagrin 166, was financially able to continue at home the treatment, consisting of rest, strict personal hygiene and nutritious diet, carefully selected and prepared. The other two were mill workers who have been compelled to return to the labor and conditions of their previous lives. It is interesting to note that these two patients, Pellagrin 113 and Pellagrin 170, showed the most extensive cutaneous eruptions observed in any of the cases and that the attack in Pellagrin 170 was the most severe one in the series. We have previously had the opportunity to observe the subsequent freedom from recurrence of patients who survive severe attacks of typhoid pellagra and we are inclined to the opinion that the disease is less likely to recur in such patients.

Two of the pellagrins died early in 1913, before the appearance of a recurrent eruption. One patient, Pellagrin 2131, has probably had

recurrence in both 1913 and 1914, although the evidence is inconclusive. The remaining eight had recurrences in 1913. One of them died early in 1914, without eruption, and seven suffered recurrence again in 1914, one dying of pellagra in November, 1914. These facts are briefly summarized in Table 18.

Among the 1,180 pellagrins in Spartanburg County were several who were treated by injections of sodium cacodylate over a considerable period. In one patient a recurrent erythema appeared on the hands during this course of treatment. We are inclined to the opinion, nevertheless, that the arsenical preparations benefit some patients,

TABLE 18.—SUMMARY OF THE RECORDS OF THE FOURTEEN PELLAGRINS TREATED AT THE POST-GRADUATE HOSPITAL IN 1912

Series No.	Pellagrin Number	Year of Onset	Termination of 1912 Attack	Record in 1913	Record in 1914
1	2131	1911	Recovery	Recurrence ?	Recurrence ?
2	1	1911	Recovery	Recurrence	Recurrence
3	2	1912	Recovery	Died early	
4	9	1910	Recovery	Died early	
5	12	1911	Recovery	Recurrence	Recurrence
6	68	1911	Recovery	Recurrence	Recurrence
7	113	1912	Recovery	Well	Well
8	114	1912	Recovery	Recurrence	Recurrence
9	21	1911	Recovery	Recurrence	Died early
10	115	1909	Recovery	Recurrence	Died of pellagra
11	153	1912	Recovery	Recurrence	Recurrence
12	166	1912	Recovery	Well	Well
13	206	1911	Recovery	Recurrence	Recurrence
14	170	1911	Recovery	Well	Well

especially if given in the interval between acute attacks; not through any specific influence on pellagra itself, but because, in a certain proportion of cases, they promote better nutrition. No doubt other tonic drugs will be found to have a similar value. The use of arsenic during the acute stages of the attack seems to us inadvisable. One advantage of hypodermic medication in pellagra is that it keeps the patient under the constant supervision of his physician and, although this feature is open to abuse as a mere pretext for collecting a fee, it is, nevertheless, of considerable importance to the well-being of the patient in many instances.

There were in this series of cases some pellagrins who were treated with the various secret nostrums, so extensively advertised as pellagra

cures in the South. Some of these patients recovered from their attack and a few have remained free from subsequent recurrences. These are the persons loudest in proclaiming the character of the treatment they had received. In one instance we had the opportunity to observe a severe recurrence in a pellagrin at the same time that his signed testimonial to the "cure" was running in the advertising pages of the local newspapers. The aspects of this business are particularly pernicious in pellagra, because of the ignorance and poverty of the majority of its victims and because the natural evolution of the disease gives in many instances an apparent justification for the claim that it has been cured.

There were in this series of 1,180 pellagrins a considerable number who changed their place of residence to a cooler climate on account of pellagra. It has not been possible for us to follow these patients in a manner sufficiently definite to warrant a detailed discussion of them. We have gained a distinct conviction, however, that pellagrins do much better in a cooler climate. This has been gained in part from the repeated histories of good health enjoyed by pellagrins who moved back to the mountains or who went north to live, and in part from the observation of improvement during a few weeks of cooler weather, in pellagrins under clinical observation, and the rapid failure of pellagrins during a prolonged hot wave. We hope to present an analysis of our data touching on the relation between pellagra and weather conditions in a subsequent communication, and although it is possible this impression may not be substantiated by the actual analysis of the facts, it is stated here as our present judgment.

For the treatment of every pellagrin during the interval between attacks of the disease it is most essential to ascertain and remove the depressing influences. These may be quite various. In institutions the most important handicap is usually dietary, as has long been known. This is also a handicap which is present in a large percentage of the noninstitutional pellagrins in Spartanburg County and we purpose to consider the individual diets of these patients at a later time. The handicap of old age has already been clearly indicated as well as the danger to pellagrous women, of childbirth during the spring and early summer.

In addition to the depressing influences mentioned above, concerning which definite tabulated data have been or will subsequently be presented, we wish to refer to other depressing or predisposing factors which have been observed so frequently in pellagrins that we regard their amelioration or removal, when present, as an important step in the treatment of pellagra. Among these are chronic alcoholism, drug addictions, pulmonary tuberculosis, overwork, chronic dysentery,

pelvic disease in women and hookworm disease in children. The relief of these conditions, when present in pellagrins, seems to us clearly indicated. Unfortunately, our records concerning the association of these conditions with pellagra are not extensive enough to warrant their statistical analysis and we shall therefore rest content with the mere statement of opinion which is based on observation and experience. We are also of the opinion that strict personal hygiene, especially in the care of the mouth and teeth, and the scrupulous avoidance of tainted or contaminated food are important measures in the treatment of pellagra and in the attempt to prevent a recurrence of the disease.

SUMMARY

1. The tendency to recurrence was approximately equal in the two sexes and in the two races considered, the percentage of years with recurrence being 62.4 for white females, 63.1 for white males, 69.4 for negro females and 64.3 for negro males.

2. The death rate in recurrent attacks was 12.3 per cent. for the whole group of pellagrins considered, being considerably below the death rate in initial attack of pellagra for the same group, which was 16.2 per cent.

3. The death rate in recurrent attacks was 9.4 per cent. for white females, 14.9 for white males, 27.9 for negro females and 44.4 for negro males, the variation corresponding roughly to the difference in mortality observed in initial attacks in these groups.

4. White girls who had their initial attack of pellagra before the age of 10 showed a recurrence rate of 46.7 per cent. Those with onset in the second decade of life had a recurrence rate of 67 per cent. and the women with onset at from 20 to 50 years suffered recurrence in 63.5 per cent. of the years for which there are recorded observations. The recurrence rates for the white males with onset in the same age periods were 44, 31.6 and 71.1 per cent., respectively.

5. Recovery from pellagra is much more frequent and more permanent in children than in adults.

6. Recurrence of pellagra after one or more years of freedom from attacks is not uncommon. This phenomenon is especially noticeable in white females of child-bearing age.

7. As compared with initial attacks, recurrences of pellagra are relatively less common in white children because of their tendency to recover and in the colored race because of their high death rate in year of initial attack. Recurrent attacks are relatively more numerous in white men over 44.

8. There is a definite indication of increased resistance to recurrence at about the age of puberty in both sexes of the white race. This resistance is very evanescent in females but continues into the third decade of life in males.

9. The hygienic-dietetic treatment has given good results as far as recovery from the acute attack is concerned. Subsequent recurrence has been observed in a large majority of such cases.

10. Pellagrins who have recovered from very severe attacks seem less liable to recurrence in subsequent years.

11. General measures to increase the resistance of the patient should be continued for at least a year after recovery from the acute attack. Physiologic rest, diet and tonic drugs, as well as strict personal hygiene, should be employed.

12. The successful treatment of complicating disorders is very important in the successful management of pellagra.

EXPERIMENTAL STUDY OF THE MONONUCLEAR CELLS OF THE BLOOD AND TISSUES

WITH SPECIAL REFERENCE TO THE SO-CALLED TRANSITIONAL CELL *

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The uncertainty that exists in regard to the large mononuclear white blood cells is probably in large part due to the diverse forms they present with the usual stains, and the scarcity of each of these forms in normal blood. The several distinct types represented in this group do not have constant morphologic characteristics demonstrable by the usual stains that admit of a differential classification among them; and only occasionally is a case encountered in which one type stands out predominantly.¹ Similarly the mononuclear wandering cells of the tissues, intimately associated with the mononuclear cells of the blood, are seen in many different forms, and although widely distributed throughout the body, each form is encountered alone in appreciable numbers only in rare pathologic conditions. The relations obtaining among these different mononuclear cells of the blood and tissues is, therefore, in some confusion and the status of each uncertain.

Some of these cells, the so-called transitionals, stand out from all the rest by reason of their content in granules of oxydase ferment, as demonstrable by the indophenol-blue reaction; and some may be recognized wherever encountered by their ability to take vital stains. It has seemed that advantage might be taken of these biologic reactions in clearing up the confusion that exists as to the identity of the different types of mononuclear cells in the blood and tissues. The following study was undertaken with this end in view.

The different forms presented by the mononuclear cells of the blood and tissues has caused a wide variation in nomenclature for cells, many of which are probably identical or closely related to each other, and this tends to deprive us of the advantage of cumulative observation by different authors. But much work has been done, and in view of

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1. Van Nuys, F.: An Extraordinary Blood, *Boston Med. and Surg. Jour.*, 1907, clvi, 390. Netousek, M.: Endothelium in Stromenden Blute, *Folia haematol.*, 1913-1914, xvii, 407. Bartlett, W. B.: Localized Leukocytosis Associated with Atypical Phagocytic Cells, *Pub. Massachusetts Gen. Hosp.*, 1908-1909, ii, 390. Evans, F. A.: Observations on the Origin and Status of the So-Called Transitional White Blood Cell, *THE ARCHIVES INT. MED.*, 1916, xvii, 1.

that on which these experiments to be reported are based, a brief résumé of the nomenclature, with discussion of the more prominent hypotheses thus far advanced, is essential.

1. Primitive Wandering Cell: This term is applied to an undifferentiated small mononuclear cell of the embryo arising from the original mesenchyme cells recognized by Saxer² and Maximow³ as the mother cell of all the hemogenous and histogenous wandering cells of the body.

2. Resting Wandering Cell: By this name Marchand⁴ designates an undifferentiated small round cell considered by him as lymphoid in origin and which, similar to the one mentioned above, is found in the tissues and gives rise to many different cell forms.

3. Clasmatocyte: Ranvier⁵ first described under this term a wandering cell of the tissues characterized by a coarse polychrome protoplasmic granulation and frequently long processes that may become separated from the cell. When first described by Ranvier this cell was believed by him to be a derivative of circulating blood elements.

4. Plasma Cell: The small round cells thus named and first described by Unna,⁶ which are seen in the tissues in great numbers under some conditions, may be readily recognized by their oval shape and excentrically placed nucleus, with coarse chromatin threads. These are considered as one type of lymphocyte⁷ which has either wandered out from the blood stream, or at least is closely related to the lymphoid elements of the blood.

5. Polyblast: Maximow, in his classic studies⁸ on the wandering cells of the tissues in inflammatory reactions, identified one type of medium-sized mononuclear constantly present, which he named polyblast. This cell is characterized by great variation in form, which can best be appreciated by reference to the pictures accompanying his articles, but it is predominantly in active tissue reactions a mononuclear round cell having a fairly heavily stained nucleus often irregular in shape, and moderately abundant protoplasm that commonly does not contain any granulation. He asserted that the polyblasts arise in part from emigrated lymphocytes and in part from clasmatocyte-like forms previously in the tissues. He further stated that these cells might become "resting wandering cells" of the tissues, might assume forms resembling the clasmatocytes or those difficult to distinguish from connective tissue elements, all of which have the power to again become round mononuclear wandering cell forms. Under the name of polyblast, Maximow postulates a definite relation between the lymphocytes of the blood and many diverse types of wandering cells, including the clasmatocyte of the tissues.

6. Adventitial Cell: This is a small, round cell, described by Marchand⁴ as occurring in the tissues, especially in the region of the blood vessels. He includes in this group the mast cell, the plasma cell, the cell of small round-cell infiltration and others, and maintains that they have the power to produce

2. Saxer, F.: Ueber die Entwicklung und den Bau der normalen Lymphdrüsen und die Entstehung der roten und weissen Blutkörperchen, *Anatomische Hefte*, 1895-1896, vi, 349.

3. Maximow, A.: Ueber die Entwicklung der Blut- und Bindegewebezellen beim Säugetierembryo, *Folia haematol.*, 1907, iv, 611.

4. Marchand, F.: Ueber Klammatocyten, Mastzellen, Phagocyten des Netzes, *Verhandl. d. deutsch. path. Gesellsch.*, 1902, iv, 124.

5. Ranvier: Des clasmatocyte, *Compt. rend. Acad. d. Sc.*, 1890, cx, 165.

6. Unna: Ueber Plasmazellen insbesondere beim Lupus, *Monatsh. f. prakt. Dermat.*, 1891, xii, 296.

7. Hertz, R.: Ueber Vorkommen, Natur und Herkunft der Plasmazellen in der Milz, *Folia haematol.*, 1912, xiii, 177.

8. Maximow, A.: *Beitr. z. path. Anat. u. z. allg. Path.*, 1903, xxxiv, 153; *Ibid.*, 1904, xxxv, 93; *Ibid.*, 1905, xxxviii, 301.

highly phagocytic cells and by further change to become leukocytoid and lymphoid cells. They migrate from the tissues into the blood stream and are in turn constantly renewed to the tissues from the blood and blood-forming organs. Marchand questions the close relationship of any of these cells to some forms included by Maximow with the polyblasts, namely, those polyblasts which, remaining in the tissues, assume forms difficult to distinguish morphologically from true fixed tissue elements, and considering the clasmatocyte a fixed tissue derivative does not include it in the class of his adventitial cells. He, in disagreement with Maximow, thus excludes from what he considers the lymphoid mononuclear wandering cells of the tissues any cell that is not readily recognized as a round mononuclear cell; but in addition to the lymphoid reaction in which the adventitial cells are prominent, Marchand recognizes a histogenous reaction,⁹ in which cells definitely related to the fixed tissue elements and entirely independent of any of the lymphoid mononuclear cells, are concerned. The cells of this histogenous reaction may also, as those of the other group, the lymphoid mononuclear wandering cells of the tissues, go over into the blood and appear there as large mononuclear cells. Whereas Maximow included with his polyblast, considered of lymphoid origin, certain wandering cells difficult to distinguish from fixed tissue elements. Marchand sharply divided these into two groups, which may roughly be classified as round cells, lymphoid, and irregular cells, histogenous in origin.

7. *Pyrrhol Cell*: These cells were first recognized as a distinct entity by their ability to take vital stains and were so named by Goldmann, who used pyrrhol blue among the first of the successful vital stains. They are intimately related to the fixed tissue elements, are of diverse form and ubiquitous in origin, but are specially conspicuous in the milky patches of the omentum, in the liver as the Kupffer cells, and in the reticulum of spleen, lymph glands and bone marrow.¹⁰ These are the cells concerned in the histogenous reaction of Marchand mentioned above, and possibly are the irregular forms included in Maximow's polyblasts.

8. *Carmin Cell*: Kiyono¹¹ used lithium carmin as a vital stain, and by this name speaks of essentially the same cells as those described by Goldmann and named pyrrhol cells. He also, with Marchand, maintains that they are active wandering cells of the tissues, concerned in various types of inflammatory reaction, and that they also wander into the blood and are seen there as part of the mononuclear group. In one communication he is inclined to include the transitionals with these histogenous cells.

9. *Histiocyte*: Thus Aschoff¹² designates those cells which he considers of histogenous origin. He includes in this group the vitally staining cells mentioned above and in agreement with Marchand believes they are seen in the blood as large mononuclears, and that they are not related to the lymphoid cells. Which of the large mononuclear cells of the blood are lymphoid and which are histogenous in origin he does not assert; but his pupil Kiyono later states¹³ that although the mother cell of the histiocytes in the tissues and the histiocytes seen in the blood is identical, the cells of this group in the blood are very scarce and a differentiation between them and the other large mononuclear cells is impossible without the vital stain. Kiyono suggests that some

9. Marchand, F.: *Ueber die Herkunft der Lymphocyten und ihre Schicksale bei der Entzündung*, Verhandl. d. deutsch. path. Gesellsch., 1913, xvi, 5.

10. Goldmann, E. E.: *Cellular Activity in Health and Disease*; *Biochemical Studies Based on New Methods of Intravital Staining*, Lancet, London, 1912, i, 1183.

11. Kiyono, K.: *Die vitale Karminspeicherung*, Jena, Gustav Fischer, 1914.

12. Aschoff, L., and Kiyono, K.: *Zur Frage der grossen Mononuclearen*, *Folia haematol.*, 1913, xv, 383.

13. Kiyono, K.: *Zur Frage der histiozystaren Blutzellen*, *Folia haematol.*, 1914, xviii, 149.

of the large mononuclear and transitional cells of the blood are transition forms of the histiocytes.

10. Macrophage: This term, familiar since Metchnikoff¹⁴ introduced it to indicate any mononuclear phagocytic cell, has been restricted by H. M. Evans¹⁵ to those cells capable of taking the vital stains. While admitting their location and supposed origin in the body as already discussed, Evans calls attention to the fact that these diverse cell forms, sometimes appearing as fixed tissue elements, sometimes as mononuclear wandering cells, have little in common except their ability to take vital stains; and by this only are differentiated from some other wandering cells and fixed tissue elements. He states that these are the cells concerned in tubercle giant cell formation,¹⁶ and, although not venturing any opinion as to their relation to any of the mononuclear wandering cells of the blood, does assert that only very rarely may they be encountered in the peripheral circulation.

11. Endothelial Leukocyte: Mallory¹⁷ in his studies on typhoid fever described the activity of certain cells believed by him to be of endothelial origin, but some of which can now be recognized as those cells capable of taking a vital stain (Pyrrhol cell, Goldmann; Macrophage, Evans). Other cells to which the term endothelial leukocyte was applied by Mallory¹⁸ are those concerned in tubercle formation, osteoclasts of bone, the mononuclear cells of serous surfaces and blood, etc. He maintains that in the tissues they are derived in part from those already in the blood as large mononuclears and in part from the endothelium of the lymphatic system.

More recently, Tschaschin,¹⁹ similarly trying to classify all the mononuclear cells of the body under one head, includes the cells of the milky patches of the omentum (vitaly staining cells), those of the serous surfaces and of the spleen and blood forming organs, the small round cells abundant in the region of the blood vessels (Marchand's adventitial cell), in fact all the cells concerned in the lymphoid and histogenous reaction of Marchand, Aschoff, etc., in one group. This composite group, corresponding closely to Mallory's endothelial leukocyte classification, Tschaschin speaks of as histogenous in origin, in that they are all derived from the fixed tissue elements of the primitive mesenchyme. He believes, however, that they are also closely related to the lymphoid system, as evidenced by the appearance in inflammation of the same polyblasts from lymphocytes and these tissue wandering cells.

12. Splenocyte: Pappenheim²⁰ recognizes as histogenous macrophages (Aschoff's histiocytes) cells which he believes are descendants of the vitaly staining cells of the omentum and elsewhere. Some of these which are fixed in the spleen and never go over into the blood he speaks of as splenocytes, and ascribes to them the function of local phagocytosis and elaboration of hemolysin.

14. Metchnikoff, E.: *Die Lehre von den Phagocyten und deren experimentelle Grundlagen*, Handbuch der Pathogenen Microorganismen, Kolle u. Wassermann, Ed. 2, 1913, ii, 655.

15. Evans, H. M.: *The Macrophages of Mammals*, Am. Jour. Physiol., 1915, xxxvii, 243.

16. Evans, H. M., Bowman, F. B., Winternitz, M. C.: *An Experimental Study of the Histogenesis of the Miliary Tubercle in Vitaly Stained Animals*, Jour. Exper. Med., 1914, xix, 298.

17. Mallory, F. B.: *Histological Study of Typhoid Fever*, Jour. Exper. Med., 1898, iii, 611.

18. Mallory, F. B.: *The Principles of Pathologic Histology*, W. B. Saunders Company, Phila., 1914, p. 37.

19. Tschaschin, S.: *Ueber die "Ruhenden Wanderzellen" und ihre Beziehungen zu den anderen Zellformen des Bindegewebes und zu den Lymphocyten*, Folia haematol., 1913-1914, xvii, 317.

20. Pappenheim, A.: *Einige Worte über Histiocyten, Splenocyten und Monocyten*, Folia haematol., 1913, xvi, 1.

13. Monocyte: Pappenheim also recognizes a hematogenous macrophage, a circulating blood mononuclear that is also a descendant of the vitally staining cell, but does not arise from those in the spleen. These he speaks of as monocytes, and although he does not admit unreservedly their identity with the wandering cell of Marchand, the macrophage of Metchnikoff, the polyblasts of Maximow, the histiocyte of Aschoff, or the Goldmann pyrrhol cell, he does class together all those mentioned by stating that his monocyte is a descendant of them.

14. Transitional Cell (Uebergangsform): This cell, incorrectly so named by Ehrlich,²¹ because, when first recognized by him as a definite entity, it was thought to be a transition form between the large mononuclear and the polymorphonuclear cells of the blood, constitutes an important part of the large mononuclear group of blood cells. It is capable of specific stimulation,²² but is not even yet generally considered as an independent cell type. When recognized at all it has been ascribed various sources of origin, endothelial (Mallory¹⁸), histogenous (Aschoff¹²), lymphoid (Pappenheim²³), and myeloid (Naegeli²⁴). It is the only mononuclear cell that contains an oxydase ferment, and to avoid confusion throughout the rest of this paper, it will be designated oxydase mononuclear.

From this brief résumé of part of the literature it is apparent that although all observers quoted admit the close embryologic relation between the connective tissue elements and the wandering cells of the tissues and blood, they are in no way in agreement as to the exact relations existing in the mature organism. Maximow, under the classification of polyblasts, relates the mononuclear cells of the tissues to the lymphoid cells of the blood, and under the same classification describes forms of wandering cells hard to distinguish morphologically from fixed tissue elements. Marchand, through his adventitial cells and derivatives, likewise associates many of the mononuclear cells of the tissues to the blood lymphocytes, but in this group includes, it seems, only mononuclear cells with regular outline, and places the irregular forms, not in the lymphoid group, as Maximow²⁵ would have it, but in a distinct histogenous system of cells. Marchand believes that these histogenous cells, although entirely distinct from the

21. Ehrlich, P.: *Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes*, A. Hirschwald, Berlin, 1891, p. 126.

22. Footnote 1, last reference.

23. Pappenheim, A.: *Ueber verschiedene Typen von Lymphozyten und Monocyten, zum Teil im scheinbar normalen Blut*, *Folia haematol.*, 1911, xii, 26.

24. Naegeli, O.: *Blutkrankheiten und Blutdiagnostik*, Veit & Co., Leipzig, 1913, p. 180.

25. One cannot be certain, of course, that the irregular cell forms seen by Maximow and classed with polyblasts and therefore to be considered of lymphoid origin, are identical with those of Marchand's histogenous group and therefore vitally staining cells, but from the description and pictures such an assumption seems justified. On the other hand, recalling that Maximow describes transformation of cells readily recognized as emigrated lymphocytes to the irregular forms under discussion, one hardly dares assume that Maximow, even in his careful study, had seen a transformation from a blood lymphocyte to a vitally staining cell, an observation so far not recorded by anyone studying these cells by means of the vital stains.

lymphoid cells, occur in the blood among the large mononuclears. Aschoff, Pappenheim, Kiyono and others similarly see distinct lymphoid and histogenous systems of wandering cells in the tissues and present in the blood in the large mononuclear group; but Pappenheim, while recognizing the cells of this histogenous group by means of the vital stain as the other observers mentioned, thinks those in the blood do not come from the vital staining cells of the spleen (splenocyte); and Kiyono believes that they are not present in great numbers in the blood. In contrast to this division of mononuclear cells into two groups, lymphoid and histogenous, may be mentioned the hypotheses of Mallory and Tschaschin, who include all the different cells in one group, according to Mallory, of endothelial, and to Tschaschin, of histogenous origin. From the literature, then, although it is manifestly unfair to interpret the opinions of the more prominent students of the subject along such narrow lines and without further exposition, one may formulate in general the following different hypotheses: that the different types of mononuclear cells of the blood and tissues are (1) lymphoid (Maximow), (2) endothelial (Mallory), (3) histogenous (Tschaschin), (4) in part histogenous and in part hematogenous (Marchand, Aschoff, Pappenheim, Kiyono).

The oxydase mononuclear (transitional) cell has not been recognized as a distinct entity in many of these studies, and has either been overlooked or included in one or the other group, and thus attributed to every possible source of origin. Pappenheim, speaking of the oxydase mononuclear cells, particularly describes them as myelolymphoidocytes,²³ yet subsequently states that they arise from the vitally staining cells in the milky patches of the omentum, where they may be seen side by side with the vitally staining cells. Kiyono suggests that the large mononuclear transitional cells are transition forms of the histiocytes. Türk²⁶ denies the relations of these oxydase mononuclear cells to the lymphoid system, and Naegeli²⁴ considers them specific myeloid elements.

EXPERIMENTAL PART

In view of the uncertainty about the genetic relations of the various mononuclear wandering cells of the tissues and the different large mononuclear cells of the blood, and the difficulty of definitely establishing this relationship by methods so far available, it was deemed advisable, ignoring this phase of the subject entirely, to attempt a classification of the adult cells of the mature organism based on the ability of the different cells to take the vital stain and to give a positive oxydase reaction. Although not definitely proved, it seems likely and is

26. Türk, W.: Vorlesungen über klinische Haematologie, W. Braumiller, Wien und Leipzig, 1904, p. 304.

generally accepted that all the cells capable of vital staining are histogenous (as compared with hematogenous) in origin and will be here so considered without further question; and for lack of a more accurately descriptive term they will be designated throughout what is to follow as *histogenous macrophages*. For the same reason any cell that does not take the vital stain will be considered of hematogenous origin and, if lacking in oxydase ferment, will be considered as ultimately derived from the lymphoid (as opposed to the myeloid) system. By the application of these two biologic reactions under conditions outlined below, whereby cells considered as histogenous (in the common acceptation as described above) may be recognized, and the commonly accepted diagnostic criteria of the lymphoid cells demonstrated, an attempt has been made to determine (1) which of the mononuclear wandering cells of the tissues, if any, are lymphoid and which histogenous; (2) which of the large mononuclear cells of the blood are lymphoid and which, if any, histogenous; (3) if the oxydase mononuclear (transitional) cells of the peripheral blood can be identified on the basis of the reactions employed with any other mononuclear cell of the blood or tissues for which well-recognized diagnostic criteria are available; and (4) whether all the mononuclear wandering cells of the body (exclusive, of course, of the true small lymphocytes) take the vital stain and are therefore after all, as some would have us believe, of histogenous origin.

Technic.—Rabbits were used in all the experiments. The total and differential white blood cell counts in these animals are subject to great variation, as already noted by Moss,²⁷ but the same cell types as in human blood are present, and there is always a good number of mononuclear cells, a large percentage of which (about 5 per cent. of the total) are typical oxydase mononuclears. Lithium carmin was used as the vital stain because of the contrast accorded with the dark-blue granules of the indophenol-blue reaction. The lithium carmin solution was used in 5 per cent. strength, and made up as advised by Kiyono.¹¹ The individual dose employed was uniformly 6 c.c. The animals were vitally stained by both intraperitoneal and intravenous injections. While the supply on hand lasted, Grubler's carmin was used, as by Kiyono in his exhaustive studies. In later experiments, because of inability to obtain Grubler's, Merck's carmin was substituted for it. As a vital stain the Merck preparation compared very favorably with that of Grubler, except that the former was more irritating and had a tendency to cause thrombosis of the ear veins after repeated injections and to call out a mild leukocytic reaction in the peritoneal cavity when

27. Moss, W. L., and Brown, G. L.: Variations in the Normal Leukocyte Count in Rabbits, *Bull. Johns Hopkins Hosp.*, 1911, xxii, 258.

injected intraperitoneally. For the demonstration of oxydase ferment the indophenol-blue reaction was used.²⁸

Intravenous Vital Staining.—To see which, if any, of the large mononuclear cells of the blood are vitally staining histogenous macrophages, animals were stained acutely and chronically by intravenous administration of the dye, and smears of blood from various vessels, tissue sections, and the omentum were studied microscopically and submitted to the oxydase reaction.

Animals chronically stained by repeated daily doses of filtered lithium carmin showed the usual distribution of carmin-stained cells in the spleen, liver, milky patches of the omentum, and bone marrow as described by Kiyono. But even when the animal was very heavily stained by more than twice the amount of stain used by Kiyono (two courses of seven daily doses separated by six days, and followed in four days by two more doses just before death) no carmin cells were seen in smears of the peripheral blood after careful search of many smears made at different periods during the course of the vital staining. This finding is in accord with results recorded by H. M. Evans,¹⁰ working with trypan blue, Goldmann,²⁹ using isamin and pyrrhol blue, and Pappenheim²⁰ and Netousek,³⁰ who state that rarely do these cells appear in the peripheral capillary circulation. Kiyono and Aschoff,¹³ using different substances, including colloidal metal suspensions, although insisting that these cells are normally seen in the peripheral blood,³¹ admit that they make up only a very small part of the large mononuclear group. However, with these heavily stained animals, or in those less heavily stained, an occasional carmin cell was seen in the smears made from the portal and splenic vein blood, but even in the most heavily stained animal they were very rare and did not seem to increase appreciably in proportion to the degree of staining. In animals thus stained none of the many carmin cells in the tissues or the

28. Evans, F. A.: The Practical Significance of the Oxydase Reaction as Applied to Blood Cells, *Proc. New York Path. Soc.*, 1915, xv, 143.

29. Goldmann, E. E.: The Process of Digestion Illustrated by the Action of Stains on the Living Tissues, *Lancet*, London, 1913, ii, 69.

30. Netousk, M.: Ueber Endothelien und ihre Beziehung zu den Monozyten, *Folia haematol.*, 1914-1915, xix, 1.

31. Kiyono did not study smear preparations of the blood, but sections of the various vessels after fixing the animal in toto in formaldehyd. By this method confusing artefactions are likely to occur, for Shipley and Cunningham (*Am. Jour. Physiol.*, 1916, xl, 75) have shown that vital stain may be absorbed through the blood vessels of the omentum and large amounts be suspended free, entirely independent of any cell, in the portal circulation. It is readily conceivable that some of this suspended material might be so placed in relation to the white blood cells in microtome sections of a formaldehyd-hardened vessel full of blood, as to simulate vital staining where in reality none was present. The possible error when intravenous injection of the stain is employed is obvious.

occasional one seen in the blood of the portal system showed a positive oxydase reaction.

A few animals were acutely stained by intravenous injection of 20 c.c. 5 per cent. filtered lithium carmin, a toxic dose that killed the animal in thirty minutes. In these no carmin cells were seen in smears made during the thirty minutes preceding death and after death from the peripheral capillary blood, from arterial blood, or from blood of the splenic and portal veins, although the plasma was a deep pink color. A few minutes after the smear was made many of the nuclei of the leukocytes took on a pink tint as they died, thus proving that the carmin was abundant enough in the plasma, even in the small amounts of it in a smear, to act as a stain.

When unfiltered lithium carmin solution, which was always opaque and showed minute particles under the microscope, was very slowly injected intravenously to avoid death by multiple embolism, often after one and almost always after two doses carmin cells might be seen in the circulating blood. But these cells uniformly gave the oxydase reaction, and with appropriate stains could be identified as polymorphonuclears and as the oxydase mononuclears of the circulating blood.

Intraperitoneal Vital Staining.—To supplement the foregoing and to determine the relations existing between the cells of the omentum and serous cavities to other wandering cells of the body and blood, animals were stained by intraperitoneal injections and studies similar to those described above were made.

Intraperitoneal injection of the filtered lithium carmin solution, even after two courses of twelve daily doses, alone or in combination with intravenous injection, gave the same results as those discussed above for the animals stained by intravenous administration of the filtered stain, except that the milky patches of the omentum were more densely stained. In several animals thus stained the omentum showed many heavily stained carmin cells that did not give the oxydase reaction, side by side with polymorphonuclear and oxydase mononuclear cells which contained no carmin stain; and in two cases the omentum was also infiltrated with many typical plasma cells which showed no carmin staining³² and did not give the oxydase reaction.

32. As already stated, cells of many different forms take the vital stains and H. M. Evans (Footnote 15) calls attention to the fact that a classification of cells based on their ability to take vital stains crosses all other lines of classification so far employed. In this connection it should be said that in these preparations containing typical plasma cells with no vital staining there were also some mononuclear cells of almost the same size that were vitally stained. This bears out Evans' statement in part and suggests that some such transition as is discussed in Footnote 25 may occur. But the observation made on these preparations can only be considered a remote suggestion of this and admits of no definite conclusion.

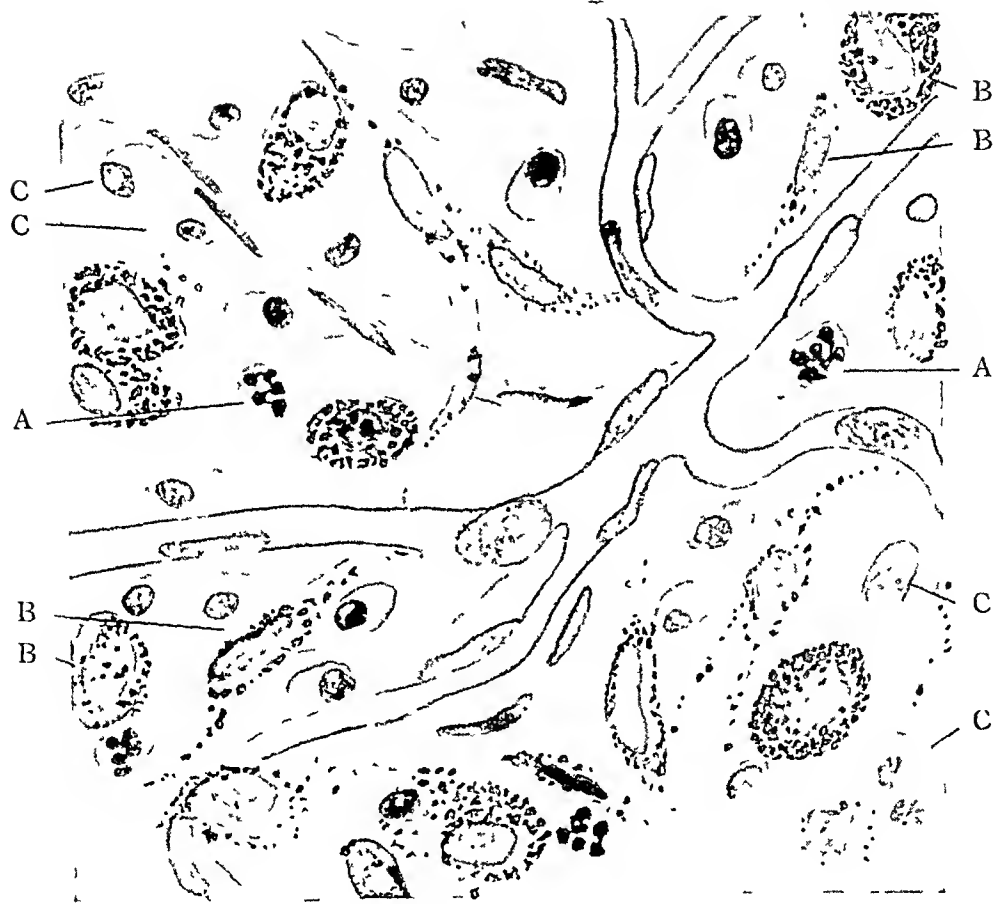


Fig. 1.—Portion of omentum from rabbit vitally stained by intravenous and intraperitoneal injection of filtered lithium carmin solution. The omentum was stretched out on a slide and stained with hematoxylin. It will be noticed that although several different types of both fixed and large wandering cells are heavily stained, the polymorphonuclear and many plasma cells present are entirely free of the stain. *A*, polymorphonuclear cells; *B*, vitally staining histogenous macrophages; *C*, plasma cells.

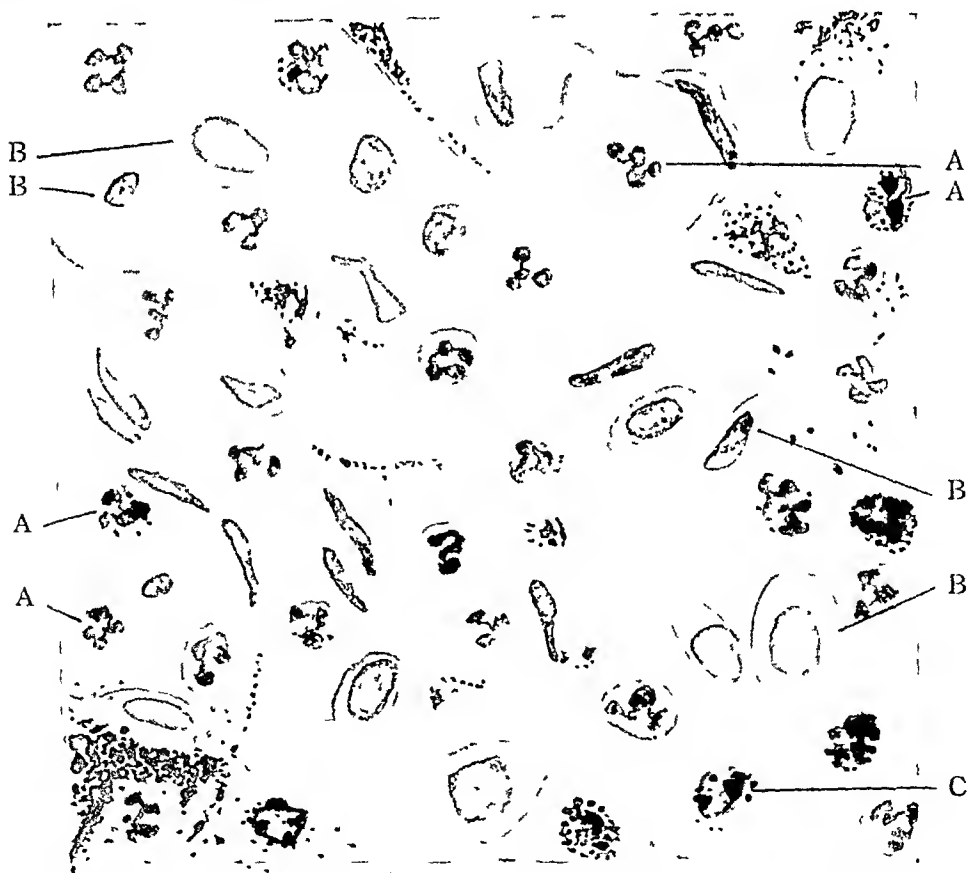


Fig. 2.—Portion of omentum from rabbit killed one hour after intraperitoneal injection of 10 c.c. unfiltered lithium carmin solution. The omentum was stretched out on a slide and stained with hematoxylin. The stain can be seen in abundance in many of the polymorphonuclear cells present, and in an oxydase mononuclear cell. The histogenous macrophages are unstained. It will be noticed that there is much free stain in the tissues. *A*, polymorphonuclear cells; *B*, histogenous macrophages; *C*, oxydase mononuclear cell.

Never were oxydase mononuclear cells seen except when the polymorphonuclear cells were numerous, and then only after careful search.

It is of further interest that in a vertical section through heavily stained milky patches of the omentum an uninterrupted layer of endothelial cells, reacting differently to carmin and having no oxydase ferment, may be seen running over their peritoneal surfaces, so that these carmin cells are separated from the peritoneal cavity by a continuous sheet of cells of a different type. These peritoneal cells do not contain carmin as compared with the abundant coarse granules of the specifically stained cells, but only a very few fine particles of this stain may be seen in their protoplasm on careful examination with highest magnification. This is in agreement with the observations of Kiyono¹¹ and of Evans¹⁰ in regard to trypan blue.

When the unfiltered stain was injected intraperitoneally, however, even after one dose and before the vitally staining histogenous macrophages had taken the stain to any extent, the polymorphonuclear and oxydase mononuclear cells in the omentum and peritoneal fluid showed many carmin granules, and under these conditions occasionally an oxydase cell with carmin granules could be found in smears of the splenic vein blood. But even when a mild leukocytic reaction in the peritoneal cavity was called out by a previous injection of weak turpentine solution, no oxydase cells were seen to contain the stain after large doses of filtered lithium carmin.³³

Mononuclear Cells in Reaction to Localized Bacterial Invasion; Experimental Pneumonia.—To study the different mononuclear cells

33. Similar experiments were undertaken with trypan blue with surprisingly different results, an observation already recorded by Pappenheim (Footnote 20). Trypan blue, a coarse colloidal suspension, differs from lithium carmin in that no particles are seen under the microscope in its unfiltered solution and yet when filtered it is not translucent as is the filtered lithium carmin. Yet no living polymorphonuclear or oxydase mononuclear cell takes up trypan blue when injected intravenously or intraperitoneally, filtered or unfiltered. Evans (Evans, H. M., and Schulemann, W.: *The Action of Vital Stains Belonging to the Benzidine Group*, Science, 1914, xxxix, 443), bases a hypothesis of the mechanism of vital staining on the size of the colloidal particle, the coarser colloidal suspensions not acting as vital stain only because of their impermeability. Colloidal metal suspensions also act as vital stain (Footnote 12), and Buxton and Torrey (Buxton, B. H., and Torrey, J. C.: *Absorption from the Peritoneal Cavity*, Jour. Med. Research, 1906, x, 5) have shown that histogenous macrophages will in time take particles as large as red blood corpuscles if made available for them by intraperitoneal injection. Thus we have the histogenous macrophage taking the finest colloidal particle or the red blood cell, and the polymorphonuclear cell refusing any colloidal particle however coarse and not active in the phagocytosis of red blood cells, yet taking microscopic masses of carmin and bacteria. Does this mean that the histogenous macrophage will take any material mass regardless of size, while the polymorphonuclear cell is selective for particles not too large or too small?

in reaction to localized bacterial invasion advantage was taken of the mononuclear character of the early exudate in pneumonia.³⁴

In the early exudates in pneumonic processes induced in rabbits by intratracheal injection of various organisms and substances after the method of Meltzer,³⁵ not only polymorphonuclear but also oxydase and nonoxydase mononuclear cells are to be seen in the exudate in great abundance.³⁴ The oxydase mononuclears are the same as those seen elsewhere; the nonoxydase mononuclears are made up of a few typical lymphocytes and other larger round cells greatly resembling the polyblast of Maximow. These cells no doubt belong to that great group of mononuclear cells seen in various inflammatory reactions throughout the body. Yet in pneumonia induced in rabbits after they had been heavily stained by combined intravenous and intraperitoneal injections of lithium carmin, neither the oxydase nor nonoxydase mononuclear cells contained the stain, and the few irregularly shaped, vitally stained cells present were either in the alveolar walls or in close association with them.

As further proof that the mononuclear cells in the early exudate in experimentally induced pneumonia in rabbits showing oxydase mononuclear and other cells resembling the polyblasts of Maximow are not vitally staining cells, pneumonia was induced in rabbits poisoned with benzol. Benzol destroys the leukopoietic tissue,³⁶ but spares the histogenous macrophages, as evidenced by the fact that in vitally stained animals rendered aleukemic by benzol administration, and in which the splenic pulp and bone marrow were largely aplastic, the milky patches of the omentum were as numerous, as cellular, and as heavily stained as in normal vitally stained animals. Yet in pneumonia induced in animals with their leukocytes thus destroyed and with their vitally staining histogenous macrophages unaffected, no cells were seen in the exudate, as already recorded by Winternitz and Hirschfelder.³⁷

Mononuclear Cells of Splenic Vein Blood.—To determine, if possible, how active a contributor to the large mononuclear cells of the blood the spleen may be, white cell counts were made of the splenic vein blood at different periods throughout these experiments; and several of these were made simultaneously with counts from the femoral veins, the right and left heart, and the peripheral capillary circulation. Tremendous variations were encountered in both the total

34. Evans, F. A.: The Cytology of the Exudate in the Early Stages in Experimental Pneumonia, Jour. Infect. Dis., 1916, xix, 440.

35. Meltzer, S. J., and Lamar, R. V.: Experimental Pneumonia by Intra-bronchial Insufflation, Jour. Exper. Med., 1912, xv, 133.

36. Selling, L.: Benzol als Leukotoxin, Beitr. z. path. Anat. u. z. allg. Path., 1911, li, 576.

37. Winternitz, M. C., and Hirschfelder, A. D.: Studies on Experimental Pneumonia in Rabbits, Jour. Exper. Med., 1913, xvii, 657.

and differential counts, so that the results were not convincing. But in agreement with Morris,³⁸ these counts all showed a higher mononuclear percentage in the splenic vein than elsewhere, quite independently of the other conditions of the experiment. Of these, a goodly number were typical oxydase mononuclears, some were suggestive of them in appearance but contained no oxydase ferment, and over half were nonoxydase mononuclears. As already stated, carmin cells in the splenic vein blood after staining with filtered lithium carmin were so rare as to be negligible in counting the total of nonoxydase mononuclear cells.

Tissue Culture of Spleen.—In the splenic pulp may be seen many oxydase and many nonoxydase mononuclear cells. In addition, many histogenous macrophages may be recognized by means of the vital stain. For the better differentiation of these cells tissue cultures of spleen³⁹ from vitally stained animals were grown in a clear medium, and cultures of spleen from a normal animal were grown in a medium containing carmin. In each of these the polymorphonuclear, oxydase mononuclear, and nonoxydase mononuclear cells that wandered out from the planted tissue during the first few days, neither contained carmin nor took it up from the medium. After these cells had died, however, on the second and third day of the original inoculation and in the transplant, many larger mononuclear cells, predominantly round, but often angular and spindle shaped, and all heavily stained with carmin, wandered out from the transplanted tissue into the surrounding medium. These cells continued to wander out even in the transplants and after active growth of the connective tissue elements which showed no stain was in progress. In many of these tissue culture preparations giant cells were formed on the cover slip. All of these were heavily stained with carmin and none showed any oxydase ferment.

Foreign Body Giant Cells in Living Animal.—For the more complete study of cells taking part in the formation of foreign body giant cells and to control the observation made in regard to them in tissue cultures, lycopodium spores were injected into the omentum and portal vein of animals that were vitally stained and received several doses of the stain after the introduction of the foreign bodies. In microscopic sections from these animals the carmin cells were relatively scanty, but in close apposition to the foreign bodies, often spread out over their surfaces. And in addition there was frequently an outer layer composed of small, round cells and larger, more irregular mono-

38. Morris, D. H.: The Rôle of the Spleen in Blood Formation, Jour. Exper. Med., 1914, xx, 379.

39. For these tissue culture preparations and help with their interpretation I am indebted to Dr. R. A. Lambert.

nuclears that did not contain the stain. None of these cells showed an oxydase ferment.

In brief, these experiments admit of the following observations:

1. Cells capable of specific vital staining by lithium carmin, the histogenous macrophages, contain no oxydase ferment; and conversely, none of the oxydase-containing cells, the polymorphonuclears and oxydase mononuclears, is specifically stained *intra vitam* by lithium carmin.

2. The polymorphonuclear and oxydase mononuclear cells phagocyte particles of carmin from the unfiltered solution long before the histogenous macrophages are vitally stained by it.

3. No normal circulating blood cell, either after acute or chronic staining of the animal by the intravenous or intraperitoneal route, takes the carmin stain; and the vitally staining histogenous macrophages are never encountered normally in the peripheral circulation, and only very rarely in the blood of the portal system.

4. In the tissues, in addition to oxydase cells of accidental occurrence, and the vitally staining histogenous macrophages normally present, there may be seen, normally and in reaction to inflammation, foreign bodies, etc., mononuclear wandering cells that contain no oxydase ferment and do not take the vital stain or phagocyte undissolved particles of it. Among these are small round cells resembling tissue lymphocytes and Marchand's adventitial cells, typical plasma cells, and other larger irregular mononuclears resembling pictures of some of Maximow's polyblasts.

5. The blood of the splenic vein contains more large mononuclear cells than blood from other sources. Many of these cells are oxydase mononuclears, but the great majority are nonoxydase mononuclears.

6. In the splenic pulp there are present polymorphonuclear, oxydase mononuclear, nonoxydase mononuclear, and vitally staining cells, each entirely distinct from all the others. The first three types are active, wandering cells and do not survive long in tissue culture preparation. The last does not migrate so actively as the other three under these conditions, survives a relatively long time in tissue culture preparations, and takes part in the formation of foreign body giant cells.

SUMMARY AND CONCLUSIONS

The application of the biologic reactions under the conditions just described, although not affording any information about the remote embryologic relation of the different mononuclear wandering cells or their complete genetic classification, does prove that they are not all of histogenous or lymphoid origin, by the generally accepted criteria, and does justify classification of the adult cells based on biologic

properties. The confusion of names encountered in the literature makes it impossible to place with certainty in this proposed classification many of the cells described, but a few forms of definite morphology, such as the plasma cell of Unna and the *Uebergangsform* of Ehrlich (oxydase mononuclear) can be assigned to one group or another without equivocation.

1. Cells containing an oxydase ferment and not taking the vital stains, the polymorphonuclear and oxydase mononuclear cells (so-called transitionals or *Uebergangsformen* of Ehrlich), primarily of the blood, but seen in the tissues under some conditions.

2. Cells containing no oxydase ferment and specifically stained intra vitam. These cells, recognized by all as intimately associated with the fixed tissue elements and variously termed histiocytes (Aschoff, Pappenheim, Marchand), pyrrhol cells (Goldmann), and macrophages (Evans), are normal constituents of the tissues and of rare and accidental occurrence in the peripheral blood. They present diverse forms in the tissues, some of which can be differentiated from cells included in the next group only by reason of their vital staining.

3. Cells containing no oxydase ferment and not taking the vital stain, the lymphoid elements. To this group belong the true lymphocytes and probably most of the nonoxydase, large mononuclears of the blood (Pappenheim's monocytes); and, in the tissues, the plasma cell of Unna, the polyblasts of Maximow, and the cell of small, round-cell infiltration.

Thus the observations made in these experiments refute the hypotheses of Mallory and Tschaschin that all the adult mononuclears of the blood and most wandering cells of the tissues are of one class, endothelial or histogenous in origin, and support the contention of Aschoff, Pappenheim, and Marchand, that there is a histogenous (capable of vital staining) and lymphoid (incapable of vital staining and containing no oxydase ferment) group distinct from each other. That many vitally staining histogenous cells are included in the large mononuclear group of blood cells, however, as asserted by Aschoff and Pappenheim, seems unlikely from the results obtained in these experiments, in which no vitally stained cells were seen in the peripheral circulation; and the fact that none of these cells anywhere contained an oxydase ferment does not support Kiyono's suggestion that the oxydase mononuclear cells are a type of the vitally staining histogenous macrophages. The higher percentage of mononuclear cells in the splenic vein blood than elsewhere is not in accord with Pappenheim's statement that the large mononuclear cells of the blood (monocytes) are not supplied in any way from the spleen; but our finding that even in the splenic vein the vitally staining histiocytes occur very rarely is in support of his belief that those of the spleen (splenocytes) are not

concerned with the large mononuclear cells of the blood. The observation here recorded that plasma cells, polyblast-like cells, cells of small round-cell infiltration, and some others in reaction to inflammation, and making up part of the cells in the region of foreign bodies, etc., do not stain vitally is not in entire agreement with Marchand, who includes many of these cells in the histogenous group; but rather, although no definite proof has been made available, since they do not contain an oxydase ferment, it appears likely that they are lymphoid cells or even changed forms of emigrated blood lymphocytes. The results obtained by applying the methods of study here employed to tissue cultures of the spleen proves a complete differentiation between the polymorphonuclear and oxydase mononuclear cells in one group, the lymphocytes and nonoxydase mononuclears in another, and the vitally staining histogenous cells in a third, as entirely justifiable in the spleen in accordance with Steudemann's views.⁴⁰

The transitional cell reacts constantly as those of the granulocyte series, in that it contains an oxydase ferment, is not specifically stained *intra vitam* and takes up carmin particles from the unfiltered solution. It may be seen in the spleen and other blood-forming organs, as admitted by all observers, but is not strikingly more abundant in the splenic vein blood than elsewhere, and is never seen in the omentum, serous fluid or tissues when no polymorphonuclear cells are present. Already sufficient evidence has been adduced that cells of this type are not seen in the uncontaminated lymph of the thoracic duct.⁴¹ These observations, therefore, lead to conclusions contrary to the opinion of Aschoff, Kiyono, Pappenheim, Mallory, Tschaschin and others, that these cells belong to the histogenous group, are lymphoid elements, or of endothelial origin; but in accordance with Naegeli, that they are of the granulocyte series, and together with the neutrophil, eosinophil and basophil, should be considered as descendants of the myeloblasts in the bone marrow and splenic pulp.

In regard to the large mononuclear group of cells as seen in the peripheral blood under normal condition, it may be said that many of them are these transitionals (oxydase mononuclear) of myeloid origin, and none are histogenous, as demonstrated by the power of vital staining. No further statement, however, can be made as to the cells making up this group. No doubt many of them are lymphoid in relation (lymphoblast, Aschoff) and probably some are small lymphocytes that have wandered in the tissues a while, have become changed in form and returned again to the blood. And there is no

40. Steudemann, K.: *Phagozytose in der Milz*, *Folia haematol.*, 1914, xviii, 140.

41. Davis, B. F., and Carlson, A. J.: *Contributions to the Physiology of Lymph*, *Am. Jour. Physiol.*, 1909-1910, xxv, 173. Lejeune, E.: *Die Zellen im Ductus lymphaticus*, *Folia haematol.*, 1914-1915, xix, 371.

reason to believe that endothelial cells may not occur in the vascular system as in other serous cavities,⁴² although no morphologic characteristics can be brought forward at present to differentiate them from the lymphoid elements.

In conclusion, therefore, although not venturing any conjecture as to the genetic relation of any one cell type to another, in regard to the adult cells seen in the mature organism it may be definitely stated that (1) the vitally staining histogenous macrophages are not normally encountered in the peripheral blood and occur in the blood of the portal system in such small numbers as to be negligible; that (2) most of the nonoxydase large mononuclear cells of the blood, and those mononuclear wandering cells of the tissues designated as plasma cells, polyblasts, and cells of small round-cell infiltration are not identical with the vitally staining histogenous macrophages, or of myeloid origin, but are probably lymphoid cells or even emigrated blood lymphocytes; and that (3) the so-called transitional cell is not a lymphocyte, any type of histogenous macrophage, or of endothelial origin, but is, with the polymorphonuclear cell, a descendant of the myeloblast and might conveniently be termed the oxydase mononuclear of normal blood.

Johns Hopkins Hospital.

42. It is not intended to convey the impression that all the cells of the serous cavities are endothelial, even under normal conditions. H. M. Evans asserts (Footnote 15) that most of them are vitally staining cells.

PHOSPHATE RETENTION AS A FACTOR IN THE PRODUCTION OF ACIDOSIS IN NEPHRITIS*

W. McKIM MARRIOTT, M.D., AND JOHN HOWLAND, M.D.

BALTIMORE

It is now a well-known and generally recognized fact that acidosis may occur in the course of nephritis, particularly in the terminal stages. Among the evidences of acidosis are a diminished carbon dioxide tension of the alveolar air, an increased hydrogen ion concentration of the blood or serum, a diminution of the alkali reserve and of the oxygen combining power of the hemoglobin.

It is not yet clear on what this acidosis depends. It is surely not due to an accumulation of the acetone bodies, for they do not appear in the urine nor are they increased in the blood. It has been suggested that lactic acid may be responsible for the acidosis. The studies of Lewis, Ryffell and others¹ have shown that lactic acid is not increased in the blood in sufficient amount to account for the acidosis. There is no direct evidence nor, so far as we are aware, is there any indirect evidence that other organic acids can be held responsible. There is a diminished ammonia excretion in many cases of severe nephritis, as Henderson and Palmer² have shown. A diminished ammonia production might well be a factor in producing acidosis. A reasonable explanation for the acidosis and one that has been suggested by a number of different writers is that the kidney fails to play its part in excreting the acid substances ordinarily formed.

The regulation of the acid base equilibrium of the body is largely brought about by the ability of the kidney to excrete acid phosphate. This regulation of reaction is one of the most important of the kidney's functions. If this function is interfered with, the normal acid base equilibrium must be disturbed and eventually acidosis is inevitable. In order to prove the failure of this function of the kidney it is neces-

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*From the Harriet Lane Home and the Department of Pediatrics of the Johns Hopkins University. -

*We have been led to the investigation of patients outside our immediate field on account of the difficulty of obtaining a sufficient number of cases of severe nephritis in children. We are much indebted to the members of the staff of the Johns Hopkins and Bay View Hospitals for furnishing us with the blood and urine of adult patients and for the use of the histories.

1. Lewis, Ryffell and others: *Heart*, 1913, v, 45.

2. Henderson and Palmer: *Jour. Biol. Chem.*, 1915, xxi, 37; *THE ARCHIVES INT. MED.*, 1915, xvi, 109.

sary to demonstrate an accumulation of inorganic phosphates in the blood serum.

Greenwald³ has determined an increase of total phosphorus in the blood serum in some cases of nephritis and with this there was often an increase in his so-called acid soluble fraction, which he believed represented chiefly inorganic phosphates. He suggested no connection between his results and the possibility of acidosis.

It has been necessary to devise a method sufficiently accurate and delicate enough to determine the inorganic phosphates in a small quantity of serum. This we have done.⁴ With this method we have determined the inorganic phosphates in the serum of a series of normal adults and older children and then of patients with nephritis, both without and with acidosis.

TABLE 1.—NEPHRITIS WITHOUT ACIDOSIS *

Case No.	Mg. per 100 C.c.		Remarks
	P	Ca	
1	5	8.3	Chronic diffuse nephritis; phenolsulphonephthalein 41 per cent in two hours; nonprotein nitrogen of blood 35 mg.; R _p H of serum 8.5; Ambard 0.146.
2	5	10	Chronic diffuse nephritis; fatal; no hyperpnea; R _p H 8.5; plasma CO ₂ 61.4; Ambard 0.137; urea nitrogen in blood 19 mg.
3	4	8	Chronic diffuse nephritis; fatal; phenolsulphonephthalein trace in two hours; R _p H 8.5; urea nitrogen in the blood 98 mg.; Ambard 0.775; plasma CO ₂ 86.
4	2.7	...	Chronic diffuse nephritis; hypertension; condition good; phenolsulphonephthalein 32 per cent. in two hours; R _p H 8.5

* The plasma carbon dioxide was determined by the Van Slyke method (Proc. Soc. Exper. Biol. and Med., 1915, xii, 165). The R_pH of the serum (alkali reserve) was determined by the Marriott method (The Archives Int. Med., 1915, xvi, 390). Phenolsulphonephthalein determinations were made on two-hour specimens. The nonprotein nitrogen and urea are expressed in terms of mg. of nitrogen per 100 gm. of blood. Chlorids are expressed in terms of sodium chlorid in grams per 100 gm. of blood. Ambard's constant is the urea constant.

The inorganic phosphate, expressed in terms of phosphorus, was low in thirty-five normal persons. The amount varied from 1 to 3.5 mg. per 100 c.c. of blood. In the great majority the amount was less than 2 mg. With marked nephritis there was a tendency for the inorganic phosphate to be slightly increased, but death from nephritis occurred in a number of patients without an increase of the phosphorus and without any evidence of acidosis.

We have determined (Table 2) the inorganic phosphate in the serum of patients with acidosis occurring in nephritis. In every instance there was an increase in the phosphorus to many times the normal amount, that is, to from 8 to 23 mg. per 100 c.c. of blood.

3. Greenwald: Jour. Biol. Chem., 1915, xxi, 29.

4. Howland, Haessler and Marriott: Jour. Biol. Chem., 1916, xxiv; Proc. xviii.

Simultaneous determinations (Table 2) of the combined carbon dioxid of the serum showed that in certain instances the phosphoric acid was combined with twice as much of the available base as was carbonic acid, in striking contrast to the normal conditions in which the base combined with phosphoric acid is only from one tenth to one fifteenth of that combined with carbonic acid.

TABLE 2.—NEPHRITIS WITH ACIDOSIS *

Case No.	Mg. per 100 C.e.		Remarks
	P	Ca	
1	22	4	Chronic diffuse nephritis; fatal; uremia; hyperpnea; R _p H 7.8; alveolar CO ₂ tension 21 mm.; nonprotein nitrogen of blood 189 mg.; Ambard 1.23; phenolsulphonephthalein 0.
2	11.3	9	Congenital polycystic kidney; improved; hyperpnea; R _p H 7.5; plasma CO ₂ 21; alveolar CO ₂ tension 25 mm.; phenolsulphonephthalein trace.
3	19	5.3	Double pyonephrosis; uremia; fatal; hyperpnea; phenolsulphonephthalein 0; urea nitrogen in blood 103 mg.; chlorids 0.538; before alkali; R _p H 7.35; plasma CO ₂ 14.7; alveolar CO ₂ tension 10.7 mm.
	12	1	After alkali; R _p H 7.9; plasma CO ₂ 36.6.
4	10.3	7.2	Chronic diffuse nephritis; fatal; nonprotein nitrogen of blood 212 mg.; hyperpnea; R _p H 7.95; plasma CO ₂ 40.
5	18	1.5	Chronic nephritis; lead poisoning; uremia; fatal; hyperpnea; phenolsulphonephthalein 0; before alkali; R _p H 7.4; plasma CO ₂ 11.
	23	4	After alkali; P _p H 7.9; plasma CO ₂ 28.
6	9	6.3	Chronic diffuse nephritis; uremia; fatal; phenolsulphonephthalein 0; R _p H 7.9; plasma CO ₂ 34.
7	8	3.3	Arteriosclerotic kidney; pneumonia; phenolsulphonephthalein 3 per cent.; fatal; R _p H 7.8; plasma CO ₂ 19.
8	9	...	Acute and chronic nephritis; fatal; hyperpnea; phenolsulphonephthalein 32 per cent.; R _p H 7.9.
9	18	3	Polycystic kidney; uremia; fatal; hyperpnea; urea in blood 332 mg.; alveolar CO ₂ 6.4 mg.; Ambard 34.8.
10	9	10	Chronic diffuse nephritis; hypertension; hyperpnea; R _p H 7.9; plasma CO ₂ 33; nonprotein nitrogen in blood 136; chlorids 0.475; Ambard 157.

* See note to Table 1.

The retention of acid phosphate (for approximately 90 per cent. of the phosphate in an average urine is acid phosphate) would seem to be sufficient to account for the degree of acidosis observed. We are not prepared to say that it is the sole factor in producing it.

The retention of acid phosphate in nephritis is not part of a general salt retention; it seems due to a certain specificity of retention, for we have found the inorganic phosphate much increased when there was no increase of sodium chlorid. It is also not necessarily proportional to the total nitrogen and urea retention. The phosphate retention is

not a result of acidosis per se, for we have failed to find an accumulation of phosphates in the serum of severe cases of acidosis in diabetes and other forms of acetone body acidosis. That the high phosphate content is due to interference with a specific function of the kidney and not to increased phosphate production in the body or increased absorption from the intestinal tract is shown by the fact that the urinary output of phosphate is not increased and indeed may be diminished. It is possible to determine a constant for phosphate excretion analogous to Ambard's constant for urea. If, as we believe, the retained phosphate is capable of doing much harm, the constant for phosphate should be of great clinical significance.

The acidosis itself may be overcome by alkali therapy, but it is a matter of experience that little besides this is accomplished. The disease usually progresses to a fatal termination. We have found that the administration of alkali generally fails to bring about a marked reduction of the accumulated phosphate; we have even observed an increase after the administration of sodium bicarbonate.

The accumulated phosphates of the serum, even though neutralized, are capable of doing serious harm to the organism. The amount is sufficient to have a definite influence on the osmotic pressure. This suggests a possible connection with the phenomena of edema and hydremia.

We have found, further, in most of the cases studied a marked reduction in the calcium of the serum. In one case this was only 1.5 mg. per 100 c.c. of serum, as compared with the normal of from 10 to 11 mg. What influence this low calcium content may have on the production of such symptoms as convulsions and hemorrhages can only be suggested. The low calcium content is to be referred to the excess of phosphates in the plasma. It has repeatedly been shown that phosphates administered in any form cause an increased elimination of calcium, chiefly by way of the intestines. The converse is also true. The administration of calcium leads to an increased elimination of phosphate, also by the bowel. This fact offers a suggestion for a rational therapeutic procedure.

VENTRICULAR RESPONSE TO AURICULAR PREMATURE BEATS AND TO AURICULAR FLUTTER*

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BOSTON

The present communication contains observations on ventricular response to auricular premature beats and to auricular flutter with especial reference to the electrocardiogram.

Auricular premature beats may be attended by normal or abnormal ventricular response, normal or aberrant complexes in the electrocardiogram. Of twenty-three patients with auricular premature beats, whose electrocardiograms were taken at the Massachusetts General Hospital, twelve showed entirely normal ventricular complexes following the abnormal auricular deflections; six showed both normal and slightly aberrant ventricular complexes; four showed normal, slightly aberrant and markedly aberrant complexes, and one showed merely slightly aberrant ventricular complexes. In the electrocardiogram of those patients showing both normal and abnormal or aberrant deflections, the earlier the premature beat the more likely it was to be followed by an abnormal ventricular complex (Figs. 1, 2 and 3). In Figure 1 the earliest premature auricular contractions are entirely blocked; those coming later are followed by abnormal ventricular complexes, and those coming latest of all are followed by entirely normal ventricular complexes.

Auricular premature beats may occur in complete heart block without influencing the ventricular rate or rhythm (Fig. 4).

In auricular flutter one ordinarily expects to find a 2 to 1 auriculo-ventricular block, with the ventricular complexes in the electrocardiogram of normal shape. In the cases collected by Ritchie twenty-nine showed 2 to 1 block and twenty-two failed to show it; most of the latter showed varying degrees of block, which produced an irregular pulse. Of twelve patients with flutter seen at the Massachusetts General Hospital five showed 2 to 1 block when first seen, while six had irregular pulses due to varying degrees of block; so far as was ascertained, only one of these six had had any digitalis and that one very little. The eleventh patient showed a 1 to 1 rhythm at the beginning of a paroxysm of flutter. After a few minutes at a very rapid rate in which the ventricles kept up with the auricles even at the

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* From the medical service of the Massachusetts General Hospital, Boston.

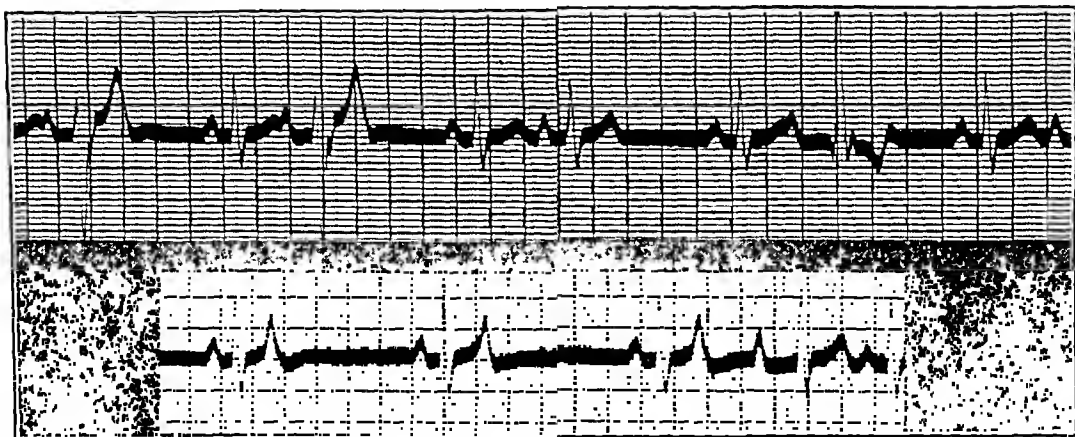


Fig. 1.—Lead II of electrocardiogram of C. S., showing numerous auricular premature beats. In the upper part of the figure the more premature beats show aberrant ventricular complexes, the less premature beat shows a normal ventricular complex. In the lower there are three auricular premature beats without ventricular response; the *P* falls on the *T*. Taken Sept. 1, 1915.

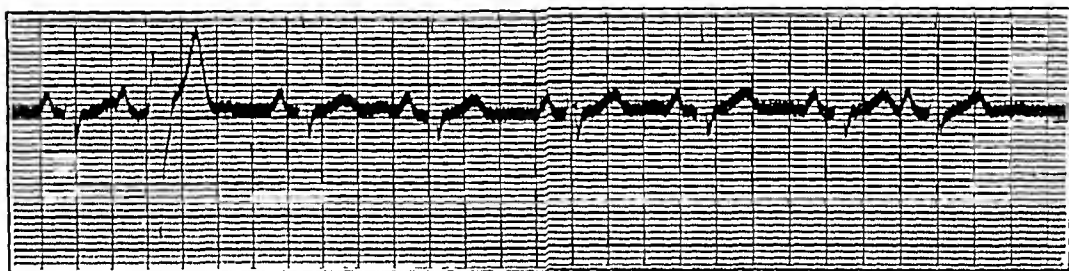


Fig. 2.—Lead II of electrocardiogram of C. S., showing two auricular premature beats. The earlier one is followed by an aberrant ventricular complex, the later by a normal ventricular complex. Taken Dec. 3, 1915.

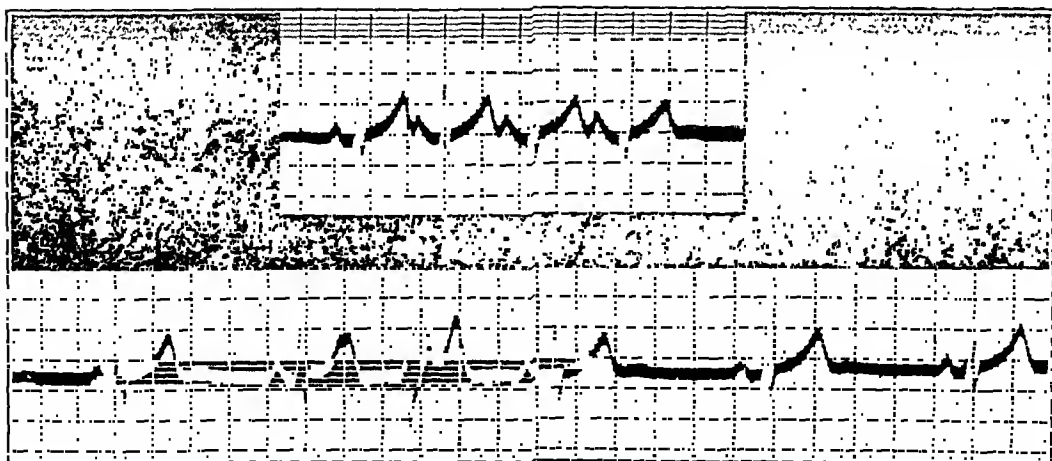


Fig. 3.—Lead II of electrocardiogram of R. M. In the upper part of the figure the premature beats show normal ventricular complexes. In the lower the very premature auricular complex, falling with the *T* deflection, is followed by a markedly delayed aberrant ventricular complex.

speed of 273 per minute, aberrant ventricular complexes suddenly appeared on the electrocardiogram (Fig. 5), suggesting an exhaustion of part of the conduction system (left branch?). Within a few minutes this gave way to a 2 to 1 auriculoventricular block, with the auricles still racing away at high speed. After a quarter hour the rhythm was found to be normal (Fig. 5). The electrocardiogram showing the onset of the change in shape of the ventricular complex is, we believe, unique. The flutter rate was rising from 231 to 273 when the change came, but the increase was gradual and there was no immediate change in rate when the newly shaped ventricular complex appeared. The interventricular intervals over the transition have been measured and found to be in seconds: 0.25, 0.24, 0.26, 0.26, 0.26, 0.23, 0.23, 0.24 | 0.23, 0.24, 0.22, 0.22, 0.22, 0.23, 0.23 . . . 0.23, 0.23, 0.24 . . . 0.24, 0.24, 0.24. The change in shape occurs at the point indicated by the vertical line. The absence of any sudden change in rate and the appearance of 2 to 1 block shortly after favor the view that the change in shape of the ventricular complex is due to aberration, rather than the view that auricular flutter has given way to ventricular flutter. During the taking of this electrocardiogram the change in movement of the string as seen on the screen of the camera suggested at the time the onset of ventricular fibrillation. The ventricular rate recorded in Figure 5 is one of the highest ever recorded graphically. Mackenzie¹ has published a polygram showing a pulse rate of 300 and Lewis² an electrocardiogram with a ventricular rate of 270.

The patient who showed the unusual electrocardiogram described above (Fig. 5) was a woman of 38 years, without other obvious abnormality of the heart, except occasional auricular premature beats. She had never suffered any important illness, with the exception of probable phthisis eight years before, of which there were no longer any definite signs. Her complaints were of nervousness, attacks of palpitation and tachycardia first occurring eighteen months before, and circulatory disturbances in the hands just coming on. Roentgen ray showed the presence of right and left cervical ribs, the right being much the larger. An operation was performed and the right cervical rib was removed. This has resulted in decided improvement in the patient's condition. Occasional auricular premature beats still occur, but no further attack of flutter has been recorded, the patient claiming to be free from all except the most transient palpitation. Her hands also have improved, but are not yet normal. The operation was performed in December, 1915.

1. Mackenzie, J.: *Diseases of the Heart*, London, 1913, p. 246.

2. Lewis, T.: *Lectures on the Heart*, New York, 1915, p. 116.

SUMMARY

Twenty-two of twenty-three patients with auricular premature beats studied electrocardiographically showed normal ventricular complexes following abnormal auricular deflections; of these twenty-two, ten showed also aberrant ventricular responses to some of the auricular premature beats; one case showed only aberrant responses. The earlier the auricular premature beat the greater the likelihood of aberration of the ventricular complex responding.

Five of twelve patients with auricular flutter showed 2 to 1 A-V block when first seen, six showed irregular pulses due to variable block, and one showed a 1 to 1 rhythm. In the latter case a remarkable transition, consisting of aberration of the ventricular complexes, occurred between the 1 to 1 and the succeeding 2 to 1 rhythms. A cervical rib seems to have been at least a contributory cause of the flutter in this case.

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ACIDOSIS IN ACUTE AND CHRONIC DISEASE *

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The term acidosis as it is used in medicine at the present time does not designate a definite clinical entity, but is applied to a variety of conditions in which, as Sellards¹ expresses it, there is a general impoverishment of the body in bases or substances which readily give rise to bases. This impoverishment in bases may be due to faulty absorption of bases, to an unusual loss of them from the body, or to their neutralization by abnormal amounts of acids. Increase in the amounts of acids in the body may be due to the production of abnormal acids, an overproduction of the usual body acids, or, as Howland and Marriott² have recently suggested, to an accumulation of normal acids due to failure in excretion.

It is difficult, if not impossible, at the present time to estimate what are the normal amounts of bases and acids in the body. Probably considerable variation occurs under different physiologic conditions. Y. Henderson recently emphasized the variations due to changes in elevation above sea level that occur in healthy subjects in some of the tests for so-called acidosis.

The methods used in testing for evidence of so-called acidosis are numerous. They consist in a direct examination of the blood, a study of the urine, a study of the products of respiration, and an estimation of the amount of alkali necessary to render the urine alkaline when administered by mouth or intravenously.

In the direct examination of the blood for evidence of so-called acidosis many studies have been made of the carbon dioxide content of the blood. It has been known for a long time that this acid diminishes in amount in the blood as other acids increase, except when variations in the excitability of the respiratory center occur, as Hasselbalch³ and others have pointed out. A diminution of the carbon dioxide

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1. Sellards: Bull. Johns Hopkins Hosp., 1914, xxv, 101.

2. Howland and Marriott: Bull. Johns Hopkins Hosp., 1916, xxvii, 63.

3. Hasselbalch: Biochem. Ztschr., 1912, xlvi, 403.

in the blood, therefore, has been looked on as evidence of acidosis. Pflüger,⁴ Senator,⁵ Geppert,⁶ and Minkowski⁷ were conspicuous among the early workers on the subject of diminished carbon dioxid in the blood in fevers. Their work, which was carried out on animals under different experimental conditions, consisted in direct examination of either the venous or the arterial blood. The lowering of the carbon dioxid content in the blood which they found in fevers was considered to be due to an increase in other acid substances. In 1889 Kraus,⁸ applying this test to man, found that the amount of carbon dioxid in the blood was diminished in fevers. He studied a few cases of typhoid fever, tuberculosis, erysipelas, scarlatina, pneumonia, and acute articular rheumatism. In 1912 Peabody⁹ studied the carbon dioxid content of the blood in pneumonia and found it usually low, occasionally normal, and rarely above normal. In the severer cases and terminal stages of the disease the carbon dioxid was usually low. Van Slyke¹⁰ has recently devised a relatively simple method for estimating the amount of carbon dioxid in the blood. This method should be of great assistance in detecting acidosis.

Studies on the hydrogen ion concentration of the blood for evidence of acidosis have been made by Peabody¹¹ in chronic nephritis and cardiac cases. He found the hydrogen ion concentration of the blood remained quite constant in his cases. Rolly¹² has made an extensive study of the hydrogen and hydroxyl ions in the blood in a variety of diseases and concludes from his observations that the alkalinity of the blood is lowered in diabetes, nephritis, severe anemia, and the gastrointestinal diseases of childhood, while, on the other hand, in diseases of the liver and in exophthalmic goiter the alkalinity of the blood is increased.

In 1888 von Jaksch¹³ reported a diminished alkalinity of the blood in uremia, fever, destructive liver disease, leukemia, chlorosis, primary anemia and carbon monoxid gas poisoning. In 1914 Sellards¹ estimated the titratable alkalinity of the blood in various conditions in which acidosis is present as shown by other tests, and found it diminished. He also found it lowered in certain chronic nephropathies and in some anemias.

4. Pflüger: *Arch. f. d. ges. Physiol.*, 1868, i, 297.

5. Senator: *Untersuchungen über fieberhaften Process und seine Behandlung*, Berlin, 1873, p. 74.

6. Geppert: *Ztschr. f. klin. Med.*, 1881, ii, 355.

7. Minkowski: *Arch. f. exper. path. u. Pharmacol.*, 1885, xix, 209.

8. Kraus: *Ztschr. f. Heilk.*, 1889, x, 106.

9. Peabody: *Jour. Exper. Med.*, 1912, xvi, 701.

10. Van Slyke: To be published in the *Jour. Biol. Chem.*

11. Peabody: *THE ARCHIVES INT. MED.*, 1914, xiv, 236.

12. Rolly: *München. med. Wchnschr.*, 1912, lix, 1201.

13. Von Jaksch: *Ztschr. f. klin. Med.*, 1888, xiii, 350.

In 1913 Marriott¹⁴ reported a method for estimating the amount of oxybutyric acid in a small amount of blood collected from a vein, and in 1914¹⁵ showed that although traces of this acid might be present in the blood during health it was increased ten to twenty fold in the acidosis of diabetes. Recently Howland and Marriott¹⁶ have reported that different acid substances, especially the acid phosphates, are increased in amount in the blood of patients with chronic nephritis.

It is to be expected that further studies on human blood will reveal cases in which normal acids are increased in amount in the blood in different diseases, or in which acids are present which are not present under normal conditions.

In considering the methods advocated for detecting the presence of acidosis by examination of the urine no attempt will be made completely to review the subject. Attention will simply be called to certain of the tests which have been used considerably of late by investigators. It must be remembered that just criticism has been raised against most of these urinary tests for acidosis, because they simply show what is excreted, and not what remains in the body. Careful studies have shown that frequently the body is unable to excrete in the urine those substances which have been looked on as indicative of acidosis.

Since Stadelmann¹⁷ discovered oxybutyric acid in the urine of diabetics in 1883, the presence of this substance or diacetic acid or acetone in the urine has been looked on as an indication of acidosis. At one time the amounts of these substances in the urine were used as indications of the degree of acidosis, but it has now been shown definitely that considerable amounts of oxybutyric acid may be present in the blood with only traces of acetone in the urine. On the other hand, there seems to be always some trace of acetone in the urine when there is much oxybutyric acid in the blood. Von Noorden¹⁸ mentions in his book that acetone has been found in scarlatina, measles, typhoid and severe dysentery. Howland and Marriott² consider that it occurs in most of the infectious diseases of childhood, just as fever occurs. In addition to the above, Taylor¹⁹ found acetone in the urine in eclampsia and phosphorus poisoning. It is also well known that acetone bodies occur in the urine in starvation and after anesthesia. Therefore acetone in the urine may be looked on as an indication that abnormal acids

14. Marriott: *Jour. Biol. Chem.*, 1913, xvi, 293.

15. Marriott: *Jour. Biol. Chem.*, 1914, xviii, 507.

16. Howland and Marriott: Reported at meeting of the American Society for the Advancement of Clinical Investigation, 1916.

17. Stadelmann: *Arch. f. exper. Pathol. u. Pharmacol.*, 1883, xvii, 419.

18. Von Noorden: *Metabolism and Practical Medicine*, Chicago Medical Book Co., 1907, ii, 160.

19. Taylor: *Digestion and Metabolism*, Lea & Febiger, Philadelphia, 1912, p. 362.

are present in the blood, but it is no indication of how large a quantity of them are present.

The relation of the amount of ammonia to the total nitrogen in the urine has been studied as an indication of excessive production of acid substances in the body. An increase in the relative amount of ammonia is looked on as an indication of so-called acidosis, although it must be borne in mind that certain diets rich in protein and diseases which cause a large breaking down of protein may show a relative as well as actual increase in ammonia nitrogen in the urine. Boussingault's²⁰ observation in 1850 that the ammonia in diabetic urines was increased was brought to the attention of medical men again in 1880 by Hallervorden.²¹ Since that time many observers have confirmed this fact and used it as a means of determining the degree of acidosis, especially in diabetes. Sellards²² has found the ammonia in the urine increased in Asiatic cholera. Pfaundler²³ reports it increased in diseases of the liver and in gastro-intestinal disorders of children. Palmer and Henderson²⁴ feel that the increase in ammonia in the urine indicates the degree of acidosis only in those cases in which the acidosis is due to the formation of oxybutyric acid. Howland and Marriott² perhaps sum up the question of the relation between a relative increase in the ammonia in the urine and acidosis by saying that such an increase suggests an acidosis, but needs confirmation by other tests.

In recent years studies have been made on the hydrogen ion concentration of the urine as estimated by Henderson's method. Henderson and Palmer²⁵ found that in certain diseases the average hydrogen ion concentration was lower than in healthy persons, but the individual variations in the different groups make the test unreliable.

Since Haldane and Priestley²⁶ in 1905 devised a relatively simple method for determining the amount of carbon dioxide in the alveolar air, this test has been much used for studies on acidosis. It is well known that the alveolar carbon dioxide corresponds closely to that in the arterial blood, and that as other acids increase this acid diminishes in amount in the blood. Thus a reduction of the tension of the carbon dioxide in the alveoli is looked on as an indication of acidosis, unless changes in the irritability of the respiratory center are present.

Von Rubow²⁷ and Beddard and Pembrey²⁸ in 1908 found a lowered

20. Boussingault: *Jour. f. prakt. Chem.*, 1850, li, 281.

21. Hallervorden: *Arch. f. exper. Path. u. Pharmacol.*, 1879-1880, xii, 237.

22. Sellards and Shaklee: *Philippine Jour. Sc.*, 1911, vi, 53.

23. Pfaundler: *Jahrb. f. Kinderh.*, 1904, lx, 719; *ibid.*, 1901, liv, 247.

24. Palmer and Henderson: *THE ARCHIVES INT. MED.*, 1913, xii, 153.

25. Henderson and Palmer: *Jour. Biol. Chem.*, 1913, xii, 393.

26. Haldane and Priestley: *Jour. Physiol.*, 1905, xxxii, 225.

27. Von Rubow: *Festschr. b. d. Einweihung der Finseinst Klinik für innere Krankh.*, 1908, p. 26.

28. Beddard and Pembrey: *Brit. Med. Jour.*, 1908, ii, 580.

carbon dioxid tension in the alveolar air in cardiac cases which showed cyanosis. Fitzgerald²⁹ also found the carbon dioxid tension in the alveolar air below normal in cases of congenital heart disease. Beddard and Pembrey²⁸ found evidence of acidosis by this test in diabetes. Porges, Leimdörfer and Markovici³⁰ confirmed this finding and found also that the carbon dioxid tension was lowered in cardiac dyspnea. Friderica and Olsen³¹ report evidence of acidosis as shown by this test in some cases of erysipelas, mumps and angina, but not uniformly. Straub and Schlayer³² in 1912 found the carbon dioxid tension diminished in the alveolar air in cases of chronic nephritis. Evidence of acidosis in certain cases of chronic nephritis as shown by this test has also been found by Peabody,³³ Porges and Leimdörfer³⁴ and others. Roth³⁵ reports evidence of diminished carbon dioxid tension in the alveolar air in cases of obesity and in certain surgical cases.

The estimation of the degree of acidosis by determining the amount of sodium bicarbonate taken by mouth or intravenously which is necessary to render the urine alkaline has been used extensively by Sellards. He³⁶ found increased tolerance to sodium bicarbonate in some of the nephropathies, Asiatic cholera, some anemias, rheumatic fever and diabetes. Palmer and Henderson²⁴ in 1913 applied the principle of this test in a somewhat different form and found evidence of acidosis in nephritis. Peabody³⁷ has also found evidence of acidosis by the so-called soda tolerance test of Sellards in nephritis.

It is evident from this short review that signs of so-called acidosis, as detected by various tests, may exist in numerous diseases. In each disease, however, all the tests may not be positive, as for example acetone may be found in diabetes and in diseases in children, while in chronic nephritis it is not present; yet all of these conditions may show the alveolar carbon dioxid lowered or the sodium bicarbonate tolerance increased. It would seem, therefore, that so-called acidosis is not due in each case to the same abnormal factors.

It has been the object of this work to study on the same case at the same time several of these tests for so-called acidosis with a view of finding out how the cases in which an acidosis is supposed to exist react to the different tests. Also, it was thought that evidence of

29. Fitzgerald: *Jour. Path. and Bact.*, 1909-1910, xiv, 328.

30. Porges, Leimdörfer and Markovici: *Ztschr. f. klin. Med.*, 1911, lxxiii, 389.

31. Friderica and Olsen: *Deutsch. Arch. f. klin. Med.*, 1912, cvii, 236.

32. Straub and Schlayer: *München. med. Wchnschr.*, 1912, lix, 569.

33. Peabody: *THE ARCHIVES INT. MED.*, 1914, xiv, 236.

34. Porges and Leimdörfer: *Ztschr. f. klin. Med.*, 1913, lxxvii, 464.

35. Roth: *Jour. Am. Med. Assn.*, 1915, lxv, 413.

36. Sellards: *Bull. Johns Hopkins Hosp.*, 1914, xxv, 141.

37. Peabody: *THE ARCHIVES INT. MED.*, 1915, xvi, 955.

acidosis might appear in certain diseases in which its presence has not as yet been expected.

For this purpose cases were selected from the wards of the Peter Bent Brigham Hospital for study. So far as possible cases were chosen which presented an uncomplicated picture of a single disease. In each case the carbon dioxid tension in the alveolar air was determined, the soda tolerance test was carried out, and the twenty-four-hour specimen of urine was examined for the presence of acetone, for its hydrogen ion concentration, for the total nitrogen and for the ammonia nitrogen.

The Plesch³⁸ method as modified by Higgins³⁹ was used for collecting the alveolar air, which was then examined by the method devised by Haldane⁴⁰ for gas analysis. That this method is satisfactory even in cases in which the patient is breathing rapidly or is unable to cooperate with the investigator has been shown by Walker and Frothingham.⁴¹ We (Walker and Frothingham) compared the results obtained by this method with the results obtained by examination of the venous blood direct, as recommended by Van Slyke, and found that they agreed very well in most cases. With this method under these conditions it seems fair to call the carbon dioxid tension normal when it falls between 39 and 45 mm. The alveolar air in each case was collected for examination at some time during the twenty-four hours in which the urine was collected or just after the twenty-four hours were up on the following morning before the soda tolerance test was started. Most of the samples of alveolar air were collected about two or three hours after a meal.

In studying the amount of sodium bicarbonate necessary to make the urine alkaline to litmus, 5 gm. at a time were given by mouth. At the end of two hours the patient voided the urine and if it was still acid the dose was repeated. If the patient was unable to void the next dose was put off until after the next urination. If the test was carried on through the night the patients were not aroused, so the intervals became longer. It usually takes from 5 to 15 gm. of sodium bicarbonate to change the reaction of a healthy person's urine from acid to alkaline. In a few cases the urine became amphoteric, in which cases the test was continued until it became definitely alkaline to litmus. This test was performed on the morning after the twenty-four-hour urine had been collected.

In the twenty-four-hour urines a small amount of toluol was used

38. Plesch: *Ztschr. f. exper. Path. u. Therap.*, 1909, iii, 380.

39. Higgins: Publication No. 203, Carnegie Inst. of Washington, 1915, p. 168.

40. Haldane: *Methods of Air Analysis*, London, Charles Griffin & Co., Ltd., 1912.

41. Walker and Frothingham: *Tr. Am. Soc. for the Advancement of Clinical Investigation*, 1916. Now published in *THE ARCHIVES INT. MED.*, September, 1916.

as a preservative. In some cases, due to contamination with feces or to errors on the part of those collecting the urines, the full twenty-four-hour amount was not obtained, but it was felt that probably these losses made little difference in the relation of ammonia to the total nitrogen.

The ammonia is recorded as ammonia nitrogen. This and the total nitrogen of the urine were estimated by Folin's⁴² method. The ammonia nitrogen is usually estimated under normal conditions at from 2 to 7 per cent. of the total nitrogen.

The hydrogen ion concentration of the urine was determined by Henderson's method and recorded as the logarithm with the minus sign omitted. Henderson and Palmer²⁵ found the average of 100 healthy cases to be P_H^+ 6.3. The presence of acetone was looked for by shaking the urine with glacial acetic acid and sodium nitroprussid and then adding ammonia. No attempt was made to determine quantitatively this substance.

The results of these studies are presented in the form of tables. Cases of the same disease are grouped together in one table and a few words of explanation are added to emphasize the interesting points. The actual date of the observation and the medical number of the patient are recorded so that by reference to the hospital records the exact condition of the patient at the time of the tests may be ascertained.

TABLE 1.—SYPHILIS

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P_H^+	Acetone	
11/ 5/15	3540	42	2.9	7.3	0	5
1/ 6/16	3857	44.2	2.8	5.9	0	10
2/17/16	4143	43.2	5.5	5.8	0	5

In Table 1 are grouped three cases of syphilis which showed evidence of a generalized infection with the spirochetes. It will be readily seen that in each case all the tests fall within normal limits and therefore no suggestion of acidosis is present.

In Table 2 are included two patients with epilepsy on whom the tests were taken between attacks, which came in only infrequent intervals. In these cases there is no evidence of acidosis in any of the tests used.

42. Folin and McCallum: Jour. Biol. Chem., 1912, xi, 523. Folin and Farmer: Ibid., 493.

Six cases of diabetes are presented in Table 3. In five of these cases it will be seen that there is evidence of acidosis and, furthermore, that each of these five cases shows variations from the normal in all of the tests used except in the hydrogen ion concentration of the urine. As will be observed in the other groups, this test shows such marked variation in the individual cases that it does not seem to be reliable as

TABLE 2.—EPILEPSY

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
11/ 3/15	3517	42.7	5.0	5.6	0	10
11/ 3/15	3514	39.1	6.3	5.8	0	10

a guide to acidosis. The remaining case was a mild case and showed no evidence of acidosis by any of the tests. If we assume that the acidosis of diabetes is due entirely to the presence of increased amounts of oxybutyric acid, we may expect that acidosis due to this cause in other diseases will give positive results with all these tests except the hydrogen ion concentration of the urine. Of course other factors than oxybutyric acid may take part in the acidosis of diabetes.

TABLE 3.—DIABETES

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
12/14/15	3738	34.7	18.2	6.2	+	35
12/15/15	3746	36.6	11.2	5.1	+	45
12/15/15	3757	34.6	18.9	below 4.7	+	65
1/ 4/16	3880	32.3	20.4	5.9	+	{ 60 amphoteric 90 total 10
1/24/16	4008	40.8	4.6	5	0	
1/25/16	3988	35.5	10.3	5.5	+	

Quite a different condition from the acidosis in diabetes is seen in the nine cases of exophthalmic goiter in Table 4. These cases represent various degrees of activity of the disease. In some of these cases the carbon dioxid tension in the alveolar air was quite high. Acetone was never present and the urine became alkaline on small amounts of sodium bicarbonate in four of the cases. The percentage of ammonia nitrogen to total nitrogen varied considerably, but in no case did it

reach 10 per cent. The hydrogen ion concentration shows variations from one end of the scale used to the other.

Eight cases of primary anemia with quite marked blood changes are shown in Table 5. Evidence of acidosis is suggested in the alveolar air and soda tolerance tests in two cases, but both of these

TABLE 4.—EXOPHTHALMIC GOITER

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H +	Acetone	
11/ 4/15	3431	54.4	2.8	7.3	0	15
11/16/15	3591	47.2	2.8	6.3	0	{ 10 amphoteric 15 total
12/16/15	3792	43.5	6.9	6.4	0	
12/16/15	3748	45.4	7.0	5.8	0	10
1/13/16	3896	47.7	2.1	4.7	0	5
1/21/16	3989	41.2	7.6	5.9	0	0
1/27/16	4040	40.9	4	7	0	5
2/ 1/16	4075	40.6	6.4	6.2	0	5
3/17/16	4311	43.9	7.3	below 4.7	0	{ 10 amphoteric 15 total

TABLE 5.—PRIMARY ANEMIA

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H +	Acetone	
10/23/15	3139	40.2	6.9	5.3	0	20
10/26/15	3435	41.2	4	6.6	0	10
11/ 9/15	3538	39.7	5.8	5.2	0	10
11/29/15	3690	39.3	5.5	5.6	0	{ 15 amphoteric 20 total
1/12/16	3863	36.7	7.5	5.6	0	
2/ 4/16	4063	42.5	6.9	6.3	0	15
2/29/16	4064	38.6	4	5.2	0	20 taking 1 c.c. di- lute HCl t.i.d.
2/29/16	4223	46.2	5.3	5.4	0	10

patients were receiving 1 c.c. of dilute hydrochloric acid three times a day. In other cases the amount of sodium bicarbonate necessary to render the urine alkaline was slightly elevated. The study of the ammonia-nitrogen ratio and the hydrogen ion concentration showed nothing remarkable. Certainly no appreciable degree of acidosis exists in this condition which is detectable by these tests.

Four of the six cases of advanced chronic nephritis in Table 6

show evidence of acidosis by the alveolar air test and the soda tolerance test. The percentage of ammonia is low in most of the cases, which agrees with observations of other workers. Whether this is due to faulty elimination or to the fact that ammonia is not used by the body to make up the deficiency in base met with in chronic nephritis is not clear. As there is no acetone in the urine it is evident that this acidosis is due to some other factor than that which is present in diabetes. The hydrogen ion concentration is fairly constant in these cases and somewhat lowered. Several other cases, not included in the table because all five of the tests could not be completed, showed a very marked reduction in the alveolar air carbon dioxid tension. In one case it was as low as 19 mm.

TABLE 6.—CHRONIC NEPHRITIS

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour ¹ Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H +	Acetone	
11/ 5/15	3507	44	6.5	6.2	0	10
11/ 8/15	3520	38.7	1	4.8	0	25+
11/ 8/15	3369	40.1	2.2	5.1	0	50
11/22/15	3597	37.8	4.3	5.1	0	10
1/21/16	3990	39.5	4.2	5.8	0	25
3/ 4/16	4253	29.9	2.8	5.5	0	40+

Twenty-one observations on fifteen cases of pneumonia are recorded in Table 7. In those cases in which two observations were made the second one was after the crisis. Several of these pneumonias terminated fatally. Although the respirations in many of these cases were elevated the results of the carbon dioxid tension determinations in the alveolar air checked up well with the estimation of carbon dioxid in the venous blood. Some of these cases during the course of the disease showed evidence of acidosis by this alveolar air test, while others showed just the reverse. This fits in with Peabody's observation on the blood in pneumonia. He found the carbon dioxid low in some, normal in some and elevated in a few. In a few of the cases the ammonia fraction of the total nitrogen in the urine was elevated appreciably above normal. The hydrogen ion concentration of the urine was quite variable, but on the whole tended to be toward the acid end of the scale. In one case acetone was present. In most of the cases during the height of the fever the amount of sodium bicarbonate necessary to render the urine alkaline was considerably increased. In the cases in which a plus sign is put after the number of grams it signifies that the sodium bicarbonate was discontinued for some

reason before the urine became alkaline. This test certainly suggests that an acidosis is present during the course of the fever in some of these cases. An interesting feature in this group is the fact that the different tests for acidosis show more variable results than in other diseases with acidosis. It suggests, therefore, that if an acidosis is present in pneumonia, it may be due to some other factors besides those that produce the acidosis in diabetes or chronic nephritis.

TABLE 7.—PNEUMONIA

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
11/13/15	3608	37.9	26.5	5.5	+	10
11/23/15	3608	39.7	8.3	6.2	0	5 convalescent
11/18/15	3630	40.3	5.8	5.4	0	55
11/23/15	3630	33.8	2.5	6.4	0	10 crisis passed, beginning em- pyema
11/19/15	3642	34.5	12.3	5.7	0	35+ discontinued
11/26/15	3677	44.2	7.6	5.1	0	40
11/29/15	3699	45.9	9.8	5.3	0	15
12/ 7/15	3699	47.6	7.7	6.1	0	15 convalescent
12/ 8/15	3744	40.6	8.1	5.2	0	35+ discontinued
12/31/15	3883	34.2	7.1	...	0	110
1/10/16	3883	44.7	3.3	5.6	0	15 convalescent
12/31/15	3882	34.7	5	...	0	30
1/10/16	3882	41.9	2.9	6	0	5 convalescent
1/ 4/16	3885	42	5.6	5.4	0	25
1/14/16	3944	38.1	10.7	6.2	0	{ 20 amphoteric 35 total 20 brochopneu- monia?
1/19/16	3965	41.6	5.6	5.2	0	
1/27/16	4046	45.1	7.5	5.1	0	
2/ 5/16	4046	45.1	6	5.4	0	15 convalescent
3/17/16	4263	36.3	11.8	5.2	0	Crisis on day 5 before toler- ance test was done
3/ 7/16	4280	43.1	3.3	4.9	0	15
3/17/16	4237	38.8	9.7	4.7	0	20

In Table 8 are ten observations made on eight cases of acute articular rheumatism. These patients were taking sodium salicylate at the time of the observations. In several of the cases evidence of acidosis was shown by the alveolar air studies, but not in all of them. In one case acetone was present and in another the ammonia was elevated to nearly 10 per cent., but in the other cases these tests showed no evidence of acidosis. Four of the cases showed an increase in the soda

tolerance test. The hydrogen ion concentration of the urine showed too marked variation to be of value in forming an opinion in this disease. It seems fair to say that some form of acidosis occurs in certain of these cases of acute rheumatism, which shows up in one or the other of these tests, but not consistently in any one.

TABLE 8.—ACUTE ARTICULAR RHEUMATISM

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
12/ 2/15	3715	33.2	5.1	5.7	0	10
12/ 7/15	3715	41	2.6	4.9	0	10 convalescent
12/ 2/15	3712	37.1	6.5	5.4	+	15
12/ 3/15	3662	35	5.1	7.1	0	20
12/ 8/15	3662	31.2	4.2	5.1	0	10
2/ 3/16	4038	33.2	6.4	5.3	0	20
3/23/16	4371	38.2	7.6	Below 4.7	0	40
3/27/16	4396	33.1	5.8	7.2	0	10
3/29/16	4417	44.5	6.4	5.6	0	20
4/21/16	4534	43.3	9.8	4.9	0	15

TABLE 9.—SUBACUTE NEPHRITIS

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
3/ 2/16	4160	39.5	7.1	6	0	10
3/22/16	4245	46.2	3.6	4.9	0	15
3/22/16	4314	48.5	2.9	5.2	0	10

TABLE 10.—LUNG ABSCESS

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
1/12/16	3834	40.4	3.2	5.6	0	15
3/ 7/16	4226	41.2	8.2	5.2	0	10

Three cases of subacute nephritis of a mild grade are presented in Table 9 and show no evidence of acidosis by any of the tests. In two the carbon dioxide tension in the alveolar air was rather high.

Two cases of lung abscess shown in Table 10 also give no evidence of acidosis.

In two cases of gastric cancer (Table 11) the amount of sodium bicarbonate necessary to render the urine alkaline was increased above normal in both. This may possibly have been due to some disturbance in absorption rather than an acidosis. Of the other tests the alveolar air suggested acidosis in one case. The ammonia was high in this case also. The hydrogen ion concentration in the urine represented the two extremes of the scale.

TABLE 11.—GASTRIC CANCER

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
3/20/16	4336	39.2	7.2	Below 4.7	0	{ 30 amphoteric 45 total
3/23/16	3799	37.4	12.8	7.1	0	{ 5 amphoteric 35 total

TABLE 12.—ADDISON'S DISEASE

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
10/29/15	3521	28.3	8.3	Below 4.7	0	35
3/11/16	4299	38.7	2.4	Below 4.7	0	15

TABLE 13.—CIRRHOSIS OF THE LIVER

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
2/ 2/16	4007	43.7	11.5	5.8	0	10
2/18/16	4170	38.2	6	5.1	0	25 (ascites)

In two cases of Addison's disease (Table 12) the carbon dioxide tension was just below the lower limit of normal. In one case the soda tolerance test showed an increase. It is interesting to note that in both the cases the hydrogen ion concentration was more acid than a P_H⁺ of 4.7, but conclusions from these two cases are hardly justifiable.

In one of the cases of cirrhosis of the liver (Table 13) the ammonia was elevated, as has been noted in diseases of the liver. In the

patient who had ascites the soda tolerance test was increased. This has been the finding in other of our cases of ascites from portal obstruction and probably has some relation to the portal obstruction rather than to an acidosis.

In Table 14 are grouped six cases of chronic cardiac disease. In these cases compensation was fairly well established as long as the patients were quiet in bed. Most of them preferred to have the head somewhat elevated. Except for a diminished carbon dioxid tension in one case and a slightly increased percentage of ammonia in another, there is no evidence of acidosis. In both these cases the other signs of an acidosis were absent. The hydrogen ion concentration of the urine showed such marked variation that no conclusions could be drawn from it.

TABLE 14.—CHRONIC CARDIAC

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine·			Sodium Bicarb., Gm.
			NH ₃ /N ₂ -N ₂ per Cent.	P _H ⁺	Acetone	
11/ 9/15	3523	34.8	3.7	6.4	0	5
11/10/15	3539	46.4	3.8	5.4	0	10
11/17/15	3632	39.1	4.8	7.4	0	5
12/28/15	3730	43.2	6.4	4.7	0	10
12/30/15	3460	40.2	11.7	4.7	0	10
1/31/16	4036	46.3	4.7	5.8	0	5

In Table 10 are grouped seventeen cases representing as many different conditions. In several of them interesting responses to the different tests are seen. In some of them quite marked evidence of acidosis occurs. Acetone was not found in any of these cases, so the type of acidosis was probably different from that found in diabetes. In the cases with an acute infection involving the kidney, in the case of probable miliary tuberculosis and in the case of typhoid fever evidence of acidosis was shown by the alveolar air study and the soda tolerance test. In two of these cases the hydrogen ion concentration of the urine showed it to be strongly acid. One case of gout was interesting, in that it showed no evidence of acidosis. The case of portal thrombosis was of interest in that it showed a high percentage of ammonia nitrogen in the urine, as is reported in liver disorders and a high sodium bicarbonate tolerance, which is probably due to the portal obstruction rather than to an acidosis. The cases of lymphatic leukemia, portal thrombosis and myxedema show a very slight reduction in the carbon dioxid tension of the alveolar air, but too slight to make one feel that any appreciable acidosis exists. The case which

suggested typhus was interesting in that the sodium bicarbonate tolerance was increased, suggesting an acidosis, while the carbon dioxide tension in the alveolar air was high, suggesting just the reverse.

From these studies it seems fair to conclude that the study of the hydrogen ion concentration in the urine is not reliable as an index of acidosis, and therefore it will not be considered further in this summary. It is also clear from this study that evidence of acidosis appears at times in certain diseases, while in other diseases no evidence of it is found. Those diseases which showed an acidosis at times by some

TABLE 15.—MISCELLANEOUS CASES

Date	Med. No.	Alveolar Air CO ₂ Ten- sion, Mm.	24-Hour Urine			Sodium Bicarb., Gm.	Diagnosis
			NH ₃ /N ₂ -N ₂ per Cent.	P _H +	Acetone		
12/21/15	3780	27.4	7.6	Below 4.7	0	80+	Acute infection in- volving kidney
10/29/15	3423	41.6	3.1	5.6	0	15	Chronic arthritis
10/27/15	3522	36.4	7.9	6.1	0	20	Typhoid fever
10/29/15	3457	28.7	2.6	Below 4.7	0	30	Probably military tu- berculosis
11/ 3/15	3559	42.2	4.6	5.6	0	20	Tumor in right kid- ney region
11/10/15	3480	42.5	9.8	5.8	0	15	Fever, mild, un- known cause
11/12/15	3566	41.7	7.8	7.3	0	10	Acute endocarditis
12/14/15	3787	41.9	5.2	5.0	0	10	Acute bronchitis
3/24/16	4359	46.7	6.4	6.4	0	10	Polycythemia
1/ 6/16	3905	39.9	7.1	5.3	0	15	Gonorrheal arthritis
1/12/16	3955	41.9	6.1	5.6	0	15	Perirenal abscess
1/24/16	4025	45.9	7.5	5.4	0	30	Typhus (?)
1/25/16	4035	43.5	3.4	6.6	0	10	Erythema nodosum
2/16/16	4166	45.9	5.4	5.2	0	15	Gout and alcohol
2/21/16	4180	38.3	5.6	4.7	0	10	Lymphatic leukemia
2/ 1/16	3281	38.5	27.8	5.8	0	65	Portal thrombosis
2/28/16	4197	38.3	5.6	6.0	0	15 amphi- 65 20 total	Myxedema

of these tests are diabetes, chronic nephritis, pneumonia, acute articular rheumatism and several acute febrile conditions in the miscellaneous group. Cases of exophthalmic goiter, epilepsy, syphilis, chronic cardiac disease, subacute nephritis, lung abscess, and many in the miscellaneous group distinctly did not show any evidence of acidosis by these tests. The results in the cases of primary anemia, gastric cancer, Addison's disease, and cirrhosis of the liver were not so clearly defined and in some of the tests suggested a slight acidosis.

It is evident from these tests that the acidosis found in diabetes

is due to different causes, in part at least, from those that produce it in other conditions. It also seems likely that the acidosis met with in different diseases is due to various causes, since the response to these tests varies somewhat in the different conditions.

Of these tests, either the estimation of the carbon dioxid tension in the alveolar air or the so-called soda tolerance test showed variation from the normal in all the cases of acidosis. They also seem to be of value in detecting the degree of acidosis.

I wish to thank most heartily Miss Barker, Miss Russell and Miss Cate, who as laboratory assistants helped me in carrying out the various estimations on the air and urines.

Peter Bent Brigham Hospital.

SENSORY DISTURBANCES OF CEREBRAL ORIGIN

CONSIDERATION OF TYPES AND OF DIAGNOSTIC ELEMENTS *

ALFRED GORDON, M.D.

PHILADELPHIA

The character of sensory disturbances caused by cerebral lesions has always been a subject of considerable scientific interest because of its importance from the standpoint of localization. In one of my former studies¹ an attempt was made to investigate cerebral sensory disorders from an extensive clinical material. Although some of the conclusions reached then did not coincide with those of some workers in the same field, nevertheless the facts observed were sufficiently suggestive to question the views of those writers who considered their conclusions as definitely established.

Throughout the present work it has been my aim to approach the problem of sensory disturbances of cerebral origin on an anatomic basis. In order to be able to draw more stable conclusions, I submitted my patients, during several years of observation, to a rigorously uniform investigation. That is, every one of the patients was examined and reexamined repeatedly by the same methods and same procedures with regard to all forms of superficial and deep sensibilities. Every one of the cases came to necropsy. The uniformity of investigation was so strictly observed that some definite diagnostic inferences are permissible.

The forms of sensations which I have investigated are tactile sensibility, the sense of superficial pain, the thermic sense, the power of localization, the muscular sense, especially in passive movements, the sense of weight, the spacing sense, orientation sense, and stereognostic sense.

Tactile sensation was tested with absorbent cotton, which, in my judgment, is the best of all methods, as it enables one to detect the least impairment. The sense of pain was tested with my precision esthesiometer.² The thermic sense was tested with extreme heat and cold, usually very hot water and ice. The power of localization was tested by having the patient tell the spot touched while his eyes were closed (naming procedure) or by having him point out the touched spot after his eyes had been closed during the touching and after the impress made on the skin had disappeared (looking procedure). The

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1. Gordon, A.: *Jour. Nerv. and Ment. Dis.*, March, 1903, xxx, 144.

2. Gordon, A.: *Jour. Am. Med. Assn.*, 1909, lii, 1257.

muscular sense was tested only for passive movements. The patient's eyes being closed, extension, flexion and rotation of each segment of the fingers, of the arm, forearm, thigh, leg and foot were performed. The orientation sense was tested either with the finger-to-nose movements or with the Blix method. The latter consists of the following procedure: The patient is either sitting or standing, with his back against an immovable object. With a pencil in the hand to be examined, he touches a mark made on paper, which is placed in front of him. This is repeated several times with open and with closed eyes. The pencil leaves a mark each time it touches the paper. The distance between these marks and the fixed point will determine the degree of the error. The spacing test consists of touching with two points of the compass or with one point after another in close succession. In the first case the distance between the two points will determine the degree of ability or inability to recognize two points. In the second case, while one point is in contact with the skin, the other is rapidly brought down on the skin. The appreciation of a double contact is thus determined. The sense of weight was determined by placing light and heavy objects on the parts of the body to be examined. Cork, pieces of lead and coins were the objects used and comparisons were drawn between the appreciation of various weights on the sound and affected sides. The stereognostic sense was tested by asking the patient to recognize the form, consistence, also the material of which objects placed in the hand were made, finally the nature and their names. The same kind and number of objects were used in all the nine cases.

CASE REPORTS

CASE 1.—A man, aged 43, gave a negative Wassermann reaction. At necropsy a tumor was found (mixed cell sarcoma) in the left basal ganglia (Fig. 1). There had been characteristic general symptoms of intracranial pressure, namely, persistent headache, vertigo, vomiting and later in the course of the disease optic neuritis. There was also a hemiparetic condition on the right side, with an increased knee-jerk and doubtful Babinski, but a certain paradoxical reflex on the same side. Objective sensations on the affected side showed marked diminution of sensibility to touch, but pain and temperature senses presented an interesting peculiarity. If with a pin one attempted to provoke pain, the response of the patient was entirely out of proportion to the degree of stimulation. The reaction was excessive, the patient flinched considerably and complained of much pain. When a similar stimulus was used on the other side, the response was by far less marked. If, on the other hand, a mildly warm object was applied to the paretic side, a very pleasurable sensation was experienced by the patient on the tested surface. If a cold object was applied, the patient complained of a very disagreeable sensation. It was therefore evident that in spite of the affected side being anesthetic, there was hyperreaction to the sense of pain and temperature.

The deep sensibilities were markedly affected and among them especially posture, passive movements and pressure. The position in which various portions of the right arm and leg were placed was not recognized correctly by the patient; gross errors were made. Passive movements with the arm and legs

were also not accurately executed. Weights placed on the arm and leg were equally not correctly recognized. Astereognosis was also present in the right hand, probably because of the defect in the other deep sensibilities.

Subjectively, the patient complained of a constant pain in the right arm and leg, which was so persistent that it would not yield to the usual remedies. At times the pain was sharp and lancinating in character. To sum up, there was the "syndrome thalamique," such as described originally by Dejerine.

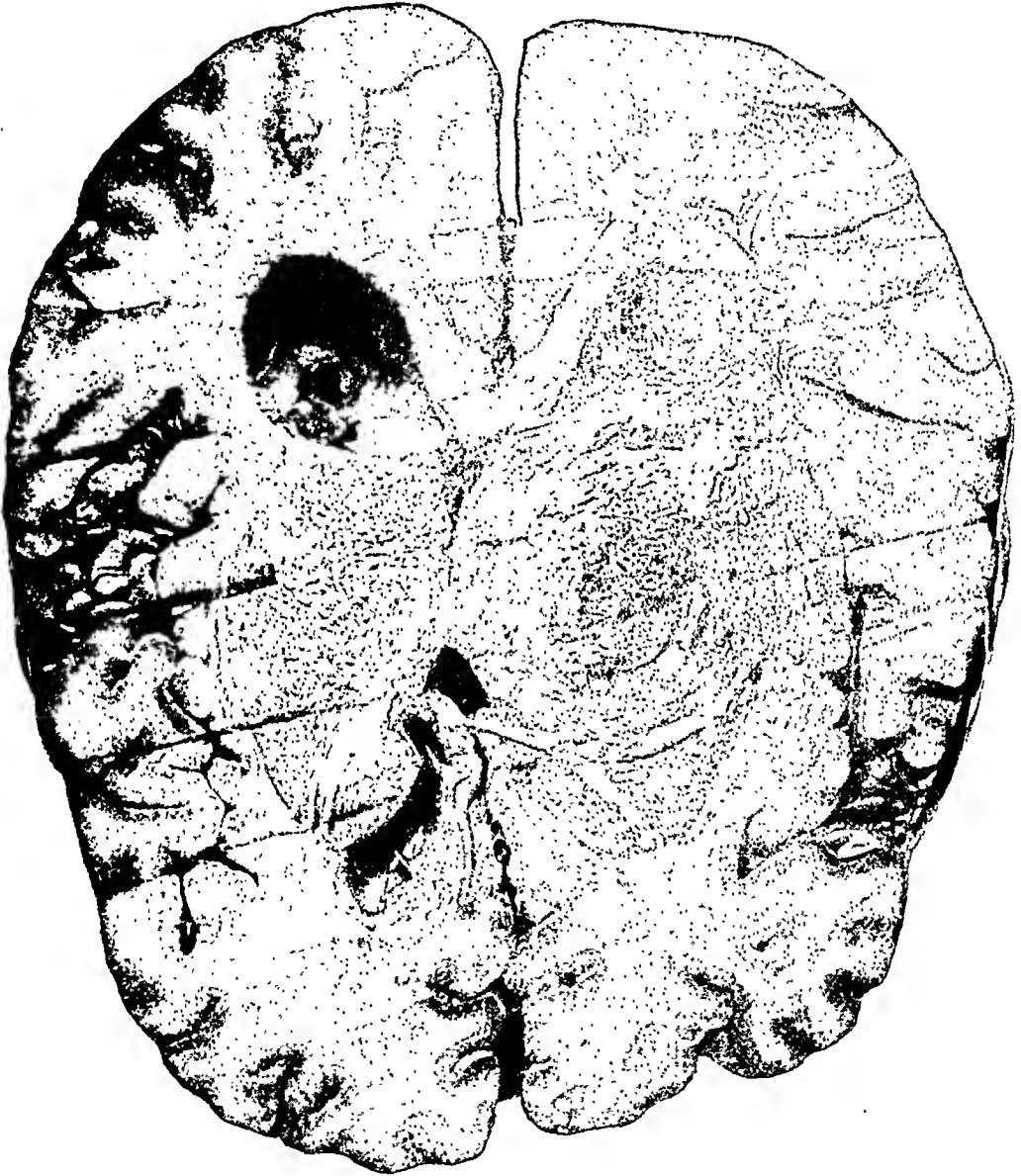


Fig. 1.—Tumor of left basal ganglia (Case 1).

CASE 2.—A man, aged 38, a laborer, gave a negative Wassermann reaction. At necropsy (Fig. 2) softening of the entire left internal capsule, including its very posterior portion, also of the lenticular and caudate nuclei and of the adjacent portion of the optic thalamus. During life there was a total right hemiplegia, with aphasia, and conjugate deviation of head and eyes to the left.

There was a distinct diminution of the cutaneous sensibility to touch, pain and temperature over the entire paralyzed side. This condition was present not only shortly after the apoplectic insult, but also before the patient died. It is interesting to observe that the sense of pain was more affected than

the sense of touch and temperature, and this was alike over both arm and leg, while on the paralyzed side of the face all three superficial sensations were equally but slightly involved. The deep sensibilities were not involved, with the exception of the muscular sense, which was only slightly impaired. When one or two fingers or the entire hand of the paralyzed side were placed in a certain position, the patient sometimes (not always) made errors. When told of the error he soon corrected it. The involvement of the muscular

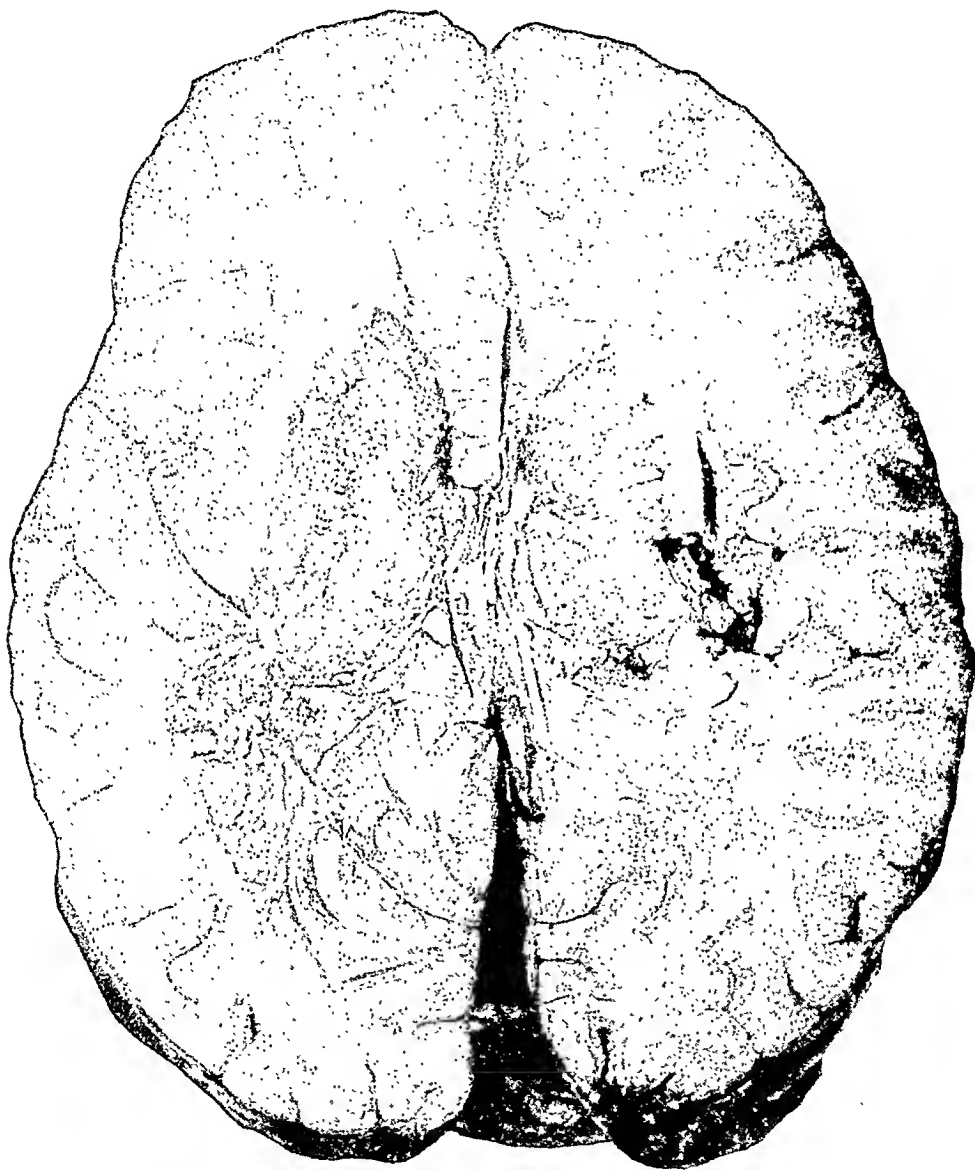


Fig. 2.—Softening of entire left internal capsule (Case 2).

sense was only distal, as this sense for the forearm, arm and shoulder remained intact. All other deep sensibilities, including the stereognostic sense, were normal. In view of the destruction of the carrefour sensitif in this patient, it is interesting to note that there was no contraction of the visual field or amblyopia on the affected side.

CASE 3.—A man, 44 years of age, gave a negative Wassermann reaction. At necropsy there was found a gliomatous tumor in the left hemisphere,

involving the supramarginal gyrus, angular gyrus and the posterior third of the first and the second temporal convolutions, also a very small portion of the occipital lobe. On section the mass was shown to extend posteriorly into the occipital lobe and mesially as far as the posterior cornu of the lateral ventricle. The very posterior portion of the internal capsule and the corona radiata were involved by the tumor (Figs. 3 and 4).

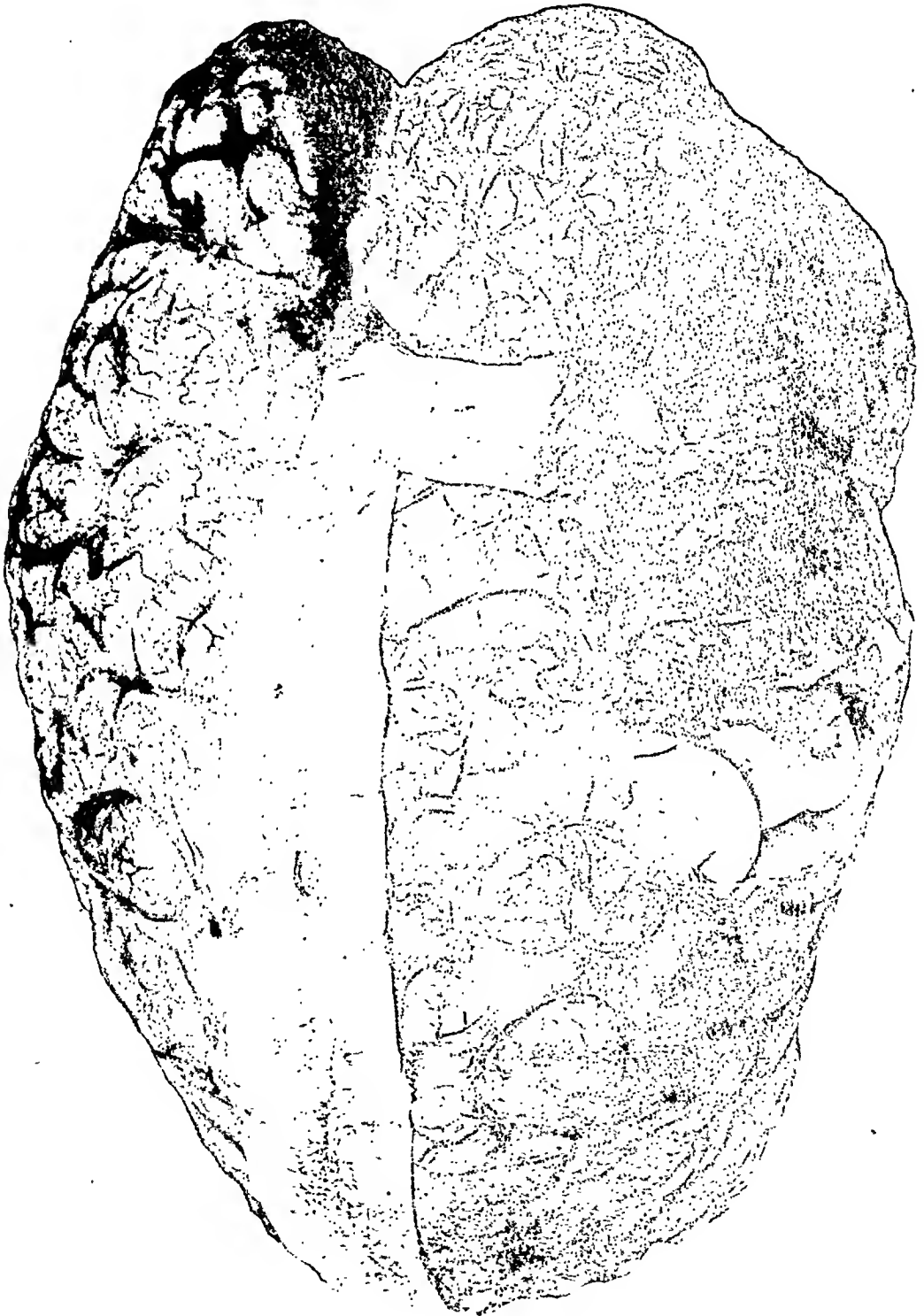


Fig. 3.—Glioma in left hemisphere, involving supramarginal gyrus, angular gyrus, posterior third of the first and the second temporal convolutions (Case 3).

During life the patient presented verbal amnesia, alexia, paraphasia and paraphagia, also retinal hemorrhages with choked disk. The motor power and reflexes were normal and equal on both sides.



Fig. 4.—Same as Figure 3.

Sensations, superficial as well as deep, were normal on both sides during the entire time of the patient's illness. At no time was astereognosis observed. The destruction of the posterior portion of the internal capsule did not produce sensory disturbances. It is also significant that in spite of the marked involvement of the inferior half of the parietal lobe and in spite of consider-

able pressure on the upper portion of this lobe, the stereognostic sense was not disturbed.

CASE 4.—A boy, 16 years of age, died from a tumor (round-cell sarcoma) wedged in between the frontal lobe and the insula of the left hemisphere and extending into the lateral ventricle in its anterior and lateral horns, compressing, displacing and destroying largely the surrounding tissue. Among the latter the lowest portions of the ascending frontal and parietal convolutions suffered considerably (Fig. 5).



Fig. 5.—Tumor (round-cell sarcoma) wedged in between the left frontal insula and the temporal lobes, penetrating the lateral ventricle (Case 4).

During life the patient presented headache, vomiting, vertigo, choked disk in both eyes, loss of knee-jerks and Achilles tendon reflexes on both sides, but Babinski and paradoxical reflexes were present on the right side. The face was slightly deviated to the left, and with this exception there was no paralysis or paresis on the right side.

On the entire right side there was a diminution of superficial sensations of all three forms, namely, touch, pain and temperature. There was no astereognosis or any other disturbance of the deep sensibilities.

CASE 5.—A man, 38 years of age, had a history of syphilis at the age of 23. Necropsy showed softening of the entire left internal capsule, lenticular nucleus, head and tail of caudate nucleus and the external capsule. The left optic thalamus was much paler than the right, and the part of it adjacent to the capsule also was softened (Fig. 6).

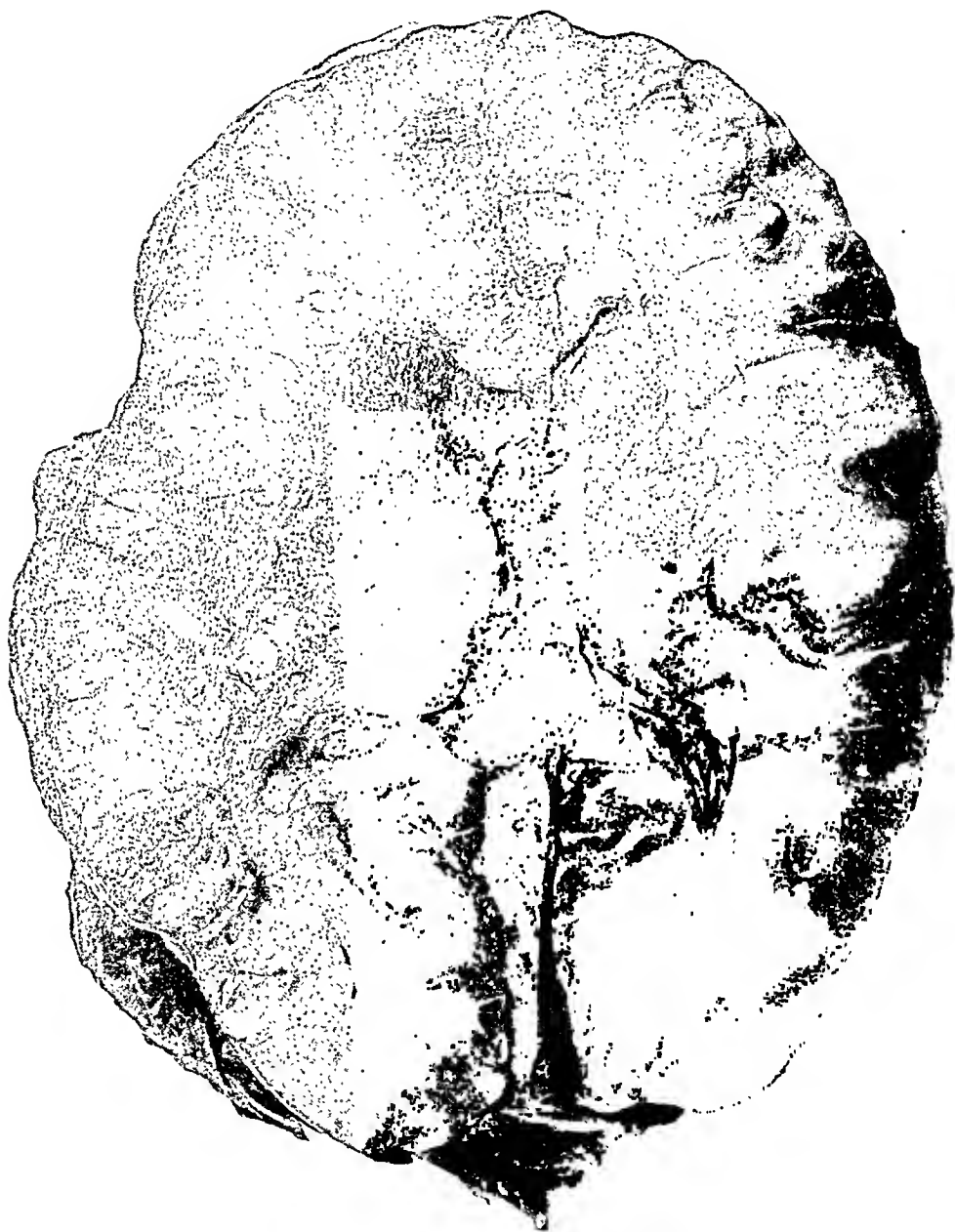


Fig. 6.—Softening of the entire left internal capsule (Case 5).

During life the patient presented a right hemiplegia with all the typical symptoms. Besides a partial alexia and partial verbal amnesia, which will not be described here, there was a decidedly marked diminution of sensations for touch, pain and temperature, also for localization. It is interesting to note that the pain sense was more involved than the touch and temperature senses, that the decrease of all sensations was more marked in the hand and foot than in the forearm and leg, and that in the latter two the diminished

sensibility was more pronounced than in the arm and thigh. The latter condition was parallel with the degree of loss of motor power in the corresponding segments of the affected limbs. The disturbance of the localization was more marked in the foot than in the hand, but an irregularity of this sensation was observed in the other parts of the right side. Thus, a touch on the right cheek was referred by the patient to the trunk, and a touch on the leg to the upper part of the thigh. Evidently the direction of pointing by the patient was toward the least-affected sensation.



Fig. 7.—Tumor of hypophysis; crura compressed; pons and medulla displaced (Case 6).

It is also interesting to observe that in spite of the destruction of the very posterior portion of the internal capsule the visual fields were not contracted, there was no amblyopia and no other special sense was involved.

CASE 6.—A man, 31 years of age, had a diagnosis made of tumor of the pituitary body. The postmortem findings showed a large vascular tumor at the base of the brain extending backward as far as the foramen magnum and

forward to the sphenoidal fissure. The tumor consisted of two portions, the anterior being the smaller, the posterior the larger. Both covered the basal portion of the brain between the orbital lobes and the pons in the middle line. It pressed backward and disfigured enormously the pons and the structure of the posterior portion of the medulla, which could be seen also on microscopic sections. The crura cerebri were compressed and deformed. Microscopic sections showed, besides the angiosarcomatous character of the

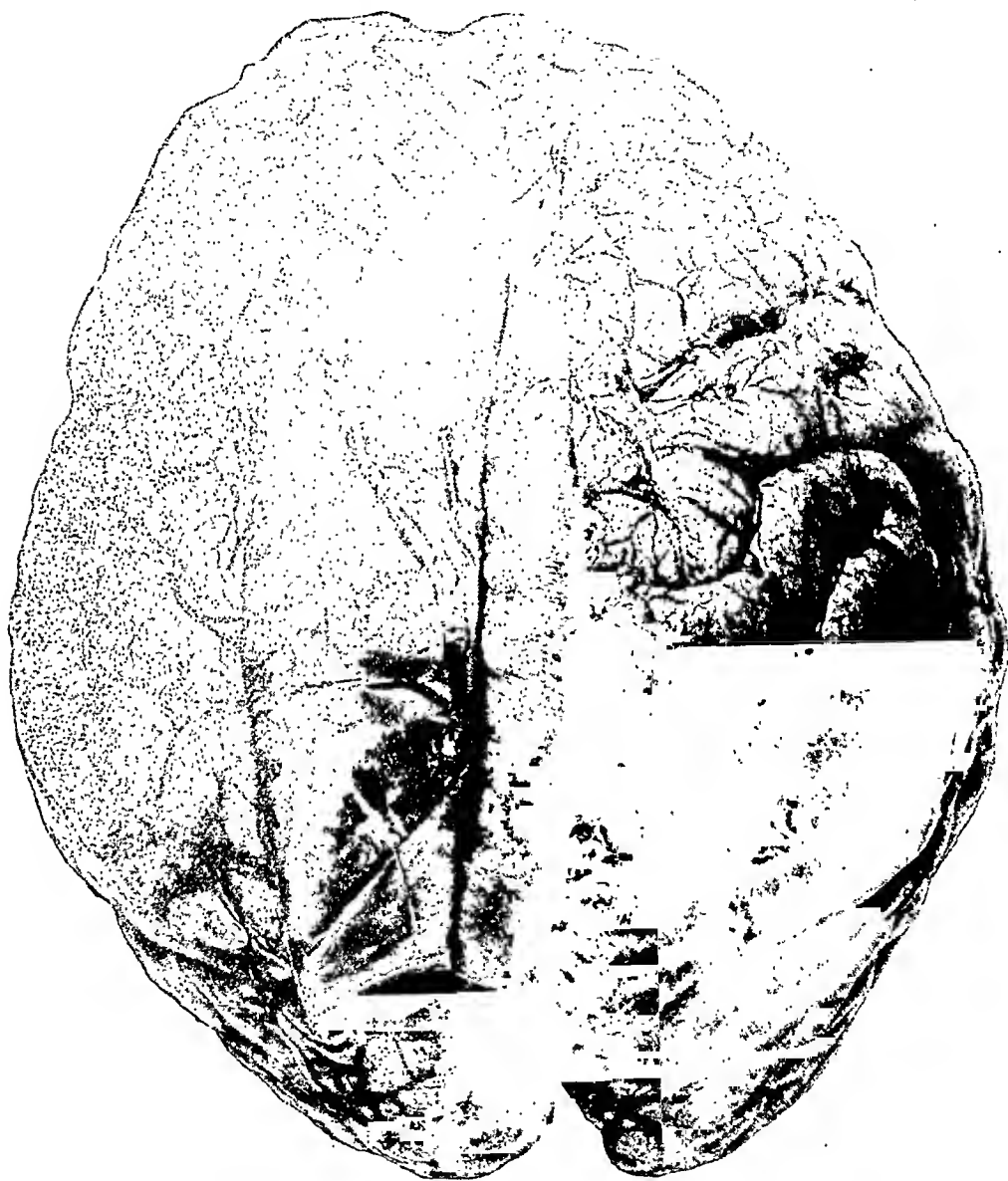


Fig. 8.—Extensive hemorrhage over right parietal lobe (Case 7).

hypophysis, also a unilateral involvement of the pyramidal tract below the cerebral peduncles and spinal cord, but not in the internal capsule. In the posterior portion of the medulla and pons all the elements were hardly distinguishable; they were displaced and deformed (Fig. 7).

The patient showed a clinical history of headache and vertigo, right exophthalma, bitemporal hemianopsia, optic atrophy in left eye and optic neuritis in the right eye, attacks of unconsciousness, glycosuria, obesity, and infantile genitalia. Gradually a left descending hemiplegia developed and convulsive

attacks made their appearance on the paralyzed side. Soon difficulty of swallowing set in.

On the left side there was a sensory dissociation of almost syringomyelic type. The tactile sense was very slightly diminished, but the sense of pain was totally abolished. The senses of heat and cold were also dissociated, the sense of cold being entirely absent, so that ice felt warm while extreme heat was taken for tepid. Astereognosis was present in the left hand, patient

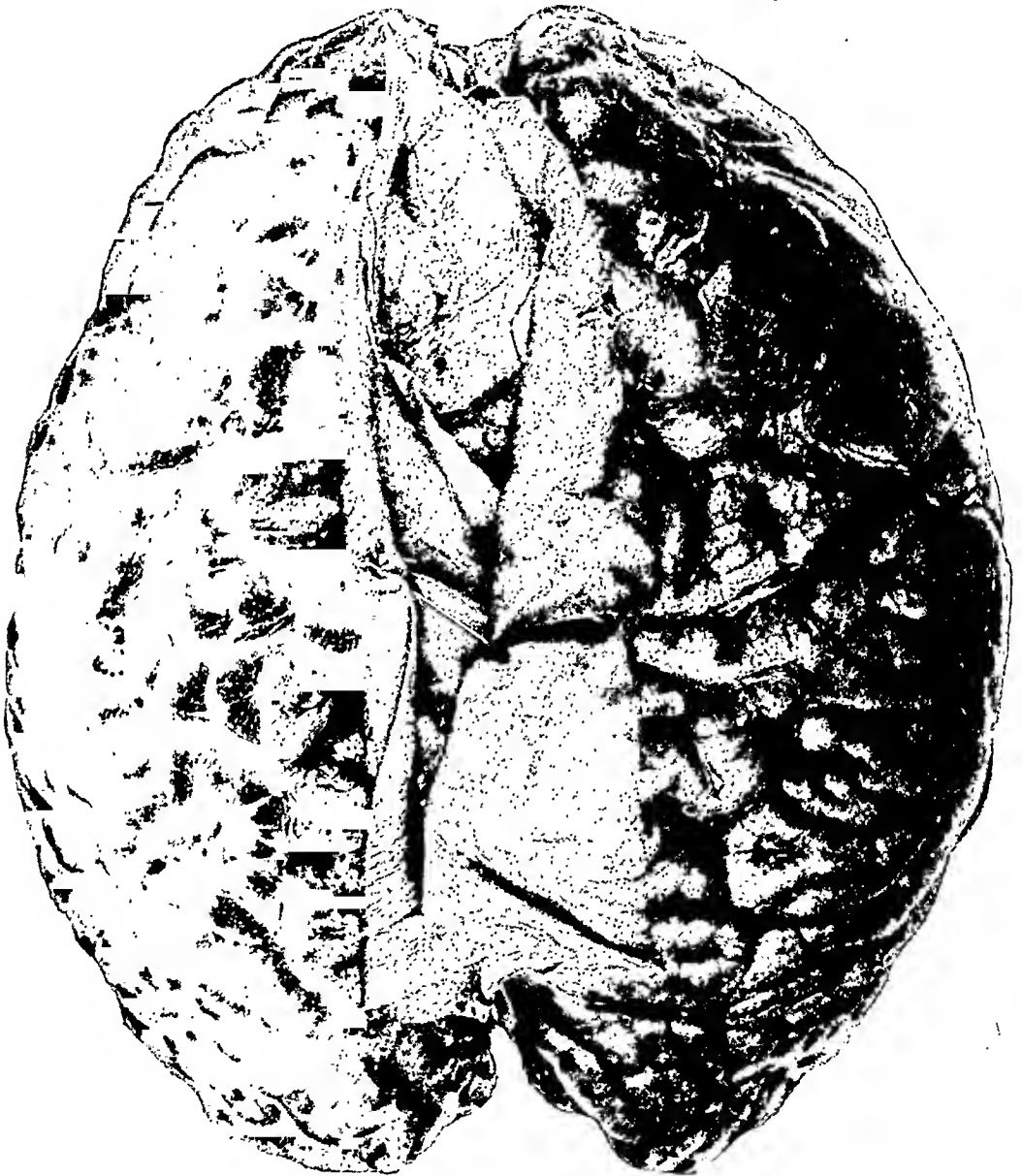


Fig. 9.—Extensive hemorrhage over right frontal lobe, encroaching on both rolandic convolutions (Case 8).

being unable to recognize the nature, shape and consistence of objects. Localization and pressure were but slightly involved. The above-mentioned diminution of the tactile sense was parallel with the loss of motor power, which was more marked in the distal than in the proximal segments of the limb and gradually decreased in intensity from the former toward the latter.

CASE 7.—A boy, aged 17, with a diagnosis of cortical hemorrhage following trauma, came to necropsy. There was a large hemorrhage over the parietal

region of the right hemisphere. The overlying portion of the meninges was thickened (Fig. 8).

The clinical history showed that the boy fell down from a third story window. He was unconscious for five hours. There was no bleeding from the facial cavities. He was found lying on his right side. Twelve hours later, when consciousness had totally returned, he was examined. There was a slightly paretic condition of the left leg and arm, more of the first than of the latter. The left knee-jerk was slightly more marked than the right and the paradoxical sign was distinct and easily obtainable on the left. The Babinski was absent.

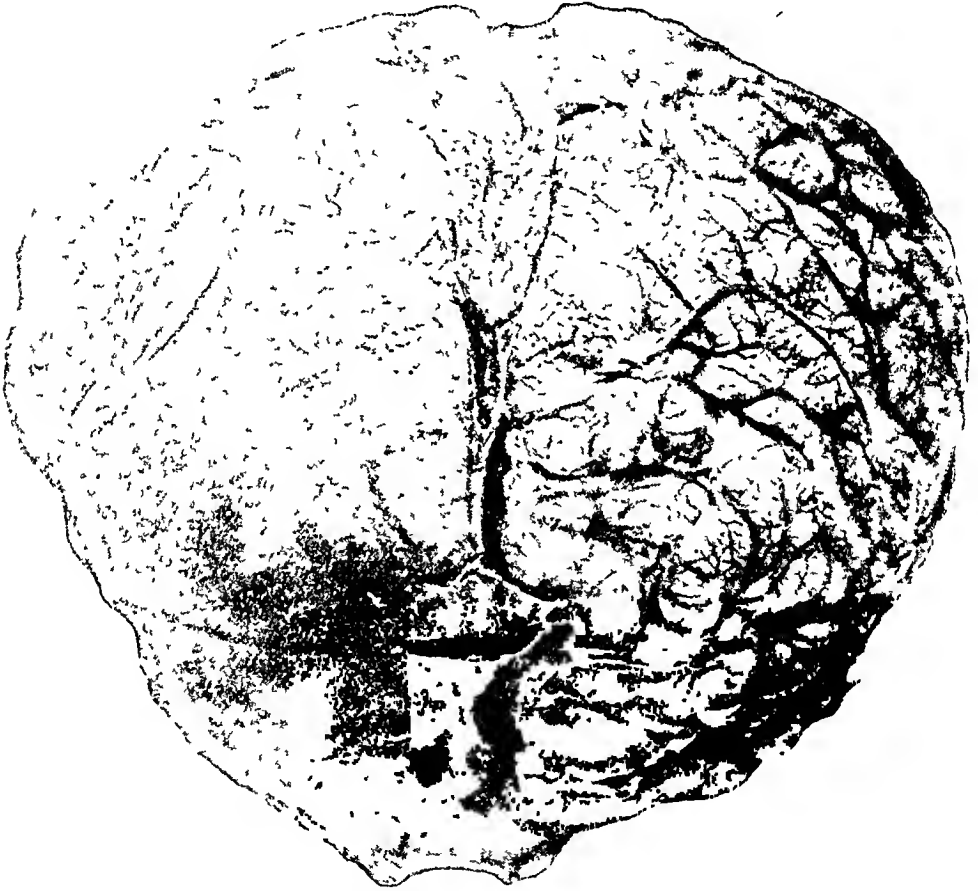


Fig. 10.—Subdural abscess over right frontal lobe, encroaching on the rolandic convolutions (Case 9).

There was a slight hemianesthesia of the left arm and leg to touch, pain and temperature. The deep sensibilities were considerably involved. Astereognosis was absolute for the left hand. The patient was unable to recognize the nature, consistence, form and material of objects placed in the left hand. Localization was markedly deficient in the left arm, hand and entire leg. Passive and active movements were equally inaccurate in the left arm and leg. Pressure, position and compass measurement were also involved, but less than the other deep sensibilities. Ataxia was distinct in his left hand, which could be demonstrated by the finger-to-nose movements and by the Blix method. The patient refused to be operated on. During his five weeks of life several examinations were made and the above sensory disturbances were found unaltered. The patient gradually developed fever and died in coma.

CASE 8.—A man, aged 32, a fireman, was injured while on duty. He was unconscious and a diagnosis of intracranial pressure in the right sensorimotor area was made.

At necropsy a large hemorrhage was found at the level of the right frontal lobe, encroaching also on the lower portions of both rolandic convolutions (Fig. 9). The patient lived two weeks. Operation was refused. He was conscious for ten days. The symptoms observed were headache and a paretic condition of the left arm and face. There was no abnormal reflex in the left leg, but the biceps and triceps reflexes of the left arm were exaggerated. The left lower face was slightly deviated to the right.

The cutaneous sensibility to touch, pain and temperature was unaltered. A slight ataxia was present in the left hand, especially in the finger-to-nose movements. Pressure, localization and compass measurements were decidedly defective in the hand, wrist and lower half of the forearm. The patient died in coma.

CASE 9.—A girl, aged 16, died from septic cerebral thrombophlebitis (pneumococcus) and abscess following an operation.

At necropsy a subdural abscess was found over the entire frontal region of the right hemisphere, encroaching on the rolandic convolutions (Fig. 10).

During life following the attack of influenza the patient developed headache, rigors, a temperature of 105, rigidity of the neck, abscess of the right upper lid and evidences of frontal sinusitis. A paretic condition of the left face, arm and leg was evident.

The sensations of touch, pain and temperature were all very slightly diminished. The left arm was ataxic and dysergic which could easily be seen in the finger-to-nose movements. Astereognosis was absolute, the patient being unable to recognize not only the form, shape and consistence but also the nature of the most ordinary objects. Position and muscular sense were defective. Other deep sensibilities, namely localization, compass measurements and pressure were all intact.

ANALYSIS OF THE CASES

Sensory Disturbances from Cortical Lesions.—In Case 4 there was a tumor pressing considerably on the lowest portions of the left ascending frontal and parietal lobes. While there was no paralysis of the right arm and leg, nevertheless there was a slight deviation of the lower portion of the face toward the left and the toe phenomenon was present. As to sensations, only the superficial ones were diminished on the entire right side. Here is an example of simultaneous involvement of the motor and sensory areas. In Case 7 a cortical hemorrhage occupied the right parietal lobe, with the result that the superficial sensations were but slightly involved, but all the deep sensibilities were strikingly affected. Among the latter the stereognostic sense especially, also the localization, muscular and orientation senses were particularly affected. Pressure, position and spacing senses were also, but to a lesser degree, involved. In Case 8 there was a hemorrhage over the right frontal lobe encroaching also on the lower portions of both rolandic convolutions. The superficial sensations were intact. Among the deep sensibilities, orientation, position, pressure, localization and spacing senses were defective in the left hand, wrist and lower half of the forearm. In Case 9 there was a subdural abscess

over the right frontal lobe encroaching on the rolandic convolutions. The superficial sensations on the left toe were very slightly diminished. Among the deep sensations, astereognosis, ataxia and dysergia were all marked on the left side; appreciation of position and muscular sense were defective, but localization, spacing and pressure were all intact.

Analysis of sensory disturbances produced by cortical lesions in these four cases demonstrates the fact that the superficial sensibilities were but slightly involved (Cases 4, 7 and 9) or not at all (Case 8); that tactile, painful and thermic senses usually run parallel in occurrence and intensity. The deep sensibilities were most constantly and always markedly affected (Cases 7, 8 and 9). Only in Case 4, in which a tumor pressed on the very lowest portions of the rolandic convolutions, the deep sensations alone were not involved. In all the three cases in which the deep sensations were defective position and muscular sense were invariably involved. Localization was intact only in one case out of three. Evidently the localization test is not always dependent on the power of an affected limb. The spacing sense was involved in but two cases. It is interesting to note that this sense runs parallel with the localization sense. In Case 9 the localization and the spacing senses were equally unaffected, but in Cases 7 and 8 they were equally affected. Astereognosis was present in two out of three cases and in both cases it was present, together with defects of some other deep sensibilities.

In considering the cortical sensory disturbances in their relation to motor phenomena we observe that in Case 4 the tumor pressed on the lower portions of both rolandic areas. Hemihypoesthesia was present, but with the exception of the left face, arm and leg, there was no motor paralysis, although Babinski's sign was present. In Case 7 motor and sensory hemianesthesias were simultaneously present. In Case 8 a hemiparetic condition was accompanied by disturbances of deep sensibilities on the same side. In Case 9 motor and sensory disturbances, superficial and deep, were equally present on the same side. We consequently find that in two cases disturbed superficial sensibility accompanied motor disorders, that in one case deep sensibilities were involved, together with the motor power, and in one case the superficial sensations were disturbed in the arm and leg, which had no loss of motor function, but there was loss of sensory and motor functions in the face. The question arises, have these findings any bearing on the sensory-motor localizations in the cortex? Do they contradict or confirm the generally accepted present view regarding the separate functions of the two ascending convolutions? In Case 4 both convolutions were compressed in their lowest portions. The tumor, being wedged in between the frontal lobe and the insula, was

located nearer the precentral than the postcentral convolutions. In spite of this the cutaneous sensibility was more involved than the motor power; there was no paralysis of the arm and leg, but a total hemianesthesia. In Case 8, on the contrary, a hemorrhage over the frontal lobe encroached also on the lower portions of both rolandic convolutions, a hemiparetic condition coexisting, with impairment of the deep sensibilities. In Case 9 there was a similar pathologic condition and sensorimotor disturbances were present. In this case all forms of sensation were involved. In these three cases both ascending convolutions were involved, consequently the problem of separate functions of the central convolutions cannot be decided from these findings. But Case 7 stands isolated from this point of view. Pathologically we find a hemorrhage covering the right parietal lobe close to the ascending parietal convolution, consequently at a distance from the ascending frontal. Clinically there were present, besides disturbed deep sensibilities, also a hemiparesis and a hemianesthesia. Moreover, the degree of the loss of both kinds of function was parallel. Here the pressure on the cortex was superficial, as sections of the affected part of the brain failed to reveal any changes in the subcortical tissue of the involved area as well as of the ascending frontal convolution. To reconcile the clinical findings in this exceptional case with the generally admitted view concerning the separate function of each rolandic convolution is quite difficult. A similar difficulty is experienced in the interpretation of many similar cases reported by competent authors. I mention at least the well-known case of Horsley (1909), in which extirpation of the ascending frontal convolution was followed by sensorimotor disturbances.

If we turn our attention to the deep sensibilities, we find in Case 7 all deep sensibilities disturbed. Pathologically the parietal lobe proper was involved. In Case 7, in spite of involvement of the lower portions of the ascending convolutions, the superficial sensations were intact and some of the deep sensibilities suffered, namely, orientation, position, pressure, localization and spacing senses. In Case 9 the pathologic condition was identical with that of Case 8 and we find a slight hemianesthesia, but a pronounced disturbance of some of the deep sensibilities, including the stereognostic sense. It is evident that all deep sensibilities are affected in cases of a lesion in the parietal lobe (Case 7), but some of them may be affected in cases of lesion in cortical areas other than the parietal, such as the frontal lobe and the two central convolutions. As far as astereognosis is concerned, we are in possession of a large number of facts, all tending to prove that the parietal lobe is not the only cortical region controlling the stereognostic function. Cases 8 and 9 are also striking examples of this contention. As to the point of view of stereognosis being a faculty

dependent on the integrity of other sensibilities, it is not tenable, as there are cases on record in which the stereognostic faculty was disturbed or abolished and other sensations were intact.³

Sensory Disorders from Capsular Lesions.—In Case 2 there was an extensive softening of the entire left internal capsule, also of the adjacent portion of the optic thalamus. The superficial sensibilities were involved over the entire paralyzed side. Among the deep sensations, only the muscular sense was slightly impaired, the others being intact. In Case 3 a gliomatous tumor involved in the left hemisphere the supramarginal gyrus, angular gyrus, and the posterior third of the first and the second temporal convolutions. On a transverse section we see the posterior portion of the internal capsule destroyed by the tumor. Apart from the special manifestations corresponding to the involved special centers, there were no sensory or motor disturbances whatever. It is also interesting to note that in spite of considerable pressure on the parietal lobe there was no trace of symptoms referable to the deep sensibilities, including the stereognostic sense. In Case 5 there was a softening of the entire left internal capsule and of the adjacent portion of the optic thalamus. The patient presented a right hemiplegia and hemianesthesia for touch, pain and temperature and also for localization. The degree of sensory diminution corresponded to the degree of diminution of the motor function, although the impairment of the localization sense was more marked in the foot than in the hand.

An analysis of these three anatomoclinical cases shows that in Cases 2 and 5 sensory and motor disturbances were concomitantly present on the same side; that in both cases the superficial sensibilities almost alone were affected; that very few of the deep sensibilities were involved, namely, muscular sense in one case and localization in the other case; that in both cases the posterior portions of the internal capsule were affected and that in both cases the adjacent portion of the thalamus was involved. In Case 3 the lesion was cortical as well as capsular. Curiously enough, the cortical lesion (parietal lobe) did not disturb the deep sensibilities and the capsular lesion (posterior limb) did not produce sensory symptoms. If, in accordance with the teaching of Charcot concerning the *carrefour sensitif*, we are to expect hemianesthesia of the cutaneous and deep sensibilities and disturbance in the domain of the special sensorium, particularly contraction of the visual fields with amblyopia on the anesthetic side, the three observations recorded speak decidedly against the alleged function of the *carrefour sensitif*. In Cases 2 and 5 there was only hemianesthesia of the superficial sensations and no involvement whatever of the

3. Gordon, A.: *Rev. Neurol.*, Sept. 30, 1910, p. 301.

special senses, and in Case 3 the posterior portion of the internal capsule was destroyed and sensory manifestations of any kind were conspicuously absent. The three cases seem to favor strongly the contention that while the internal capsule possesses a sensorimotor function, its very posterior portion does not possess the exclusive sensory function, as advocated by Türck and Charcot. This is particularly seen from Case 3. The concomitance of a lesion in that portion of the thalamus which is adjacent to the internal capsule is very significant, as it leads to the possibility if not probability that the sensory disturbances accompanying motor paralysis are due to the involvement of the corticopetal or thalamocortical fibers, which, together with the projection fibers, enter into the formation of the posterior segment of the internal capsule.

Sensory Disturbances from Lesions of the Optic Thalamus.—In Case 1 (tumor in basal ganglia in left hemisphere) there was a hemiparesis and sensory disturbances on the same side. Touch sense was diminished, but pain sense was increased (hyperalgesia); warmth produced a pleasurable sensation, cold a disagreeable sensation. On the same side some of the deep sensibilities were involved, namely, position, muscular sense, stereognostic sense and pressure. Gross errors were made by the patient at each repeated test. There was also considerable subjective pain in the right arm, which was unusually persistent.

The striking peculiarity about this case is the dissociation of the superficial sensibilities and the excessive response to painful stimuli and to cold. The existence of hyperalgesia on the anesthetic side is unusual, although sensory disorders of this character in lesions of the lateral zone of the optic thalamus have been reported by Edinger⁴ and Roussy.⁵ The pleasurable sensation to warmth and disagreeable sensation to cold form another peculiarity in this case. The fact that these phenomena, together with the above-mentioned hyperalgesia, have been totally absent in all the other cases of my series renders the condition quite suggestive, inasmuch as it may be considered characteristic of thalamic lesions.

In addition to these manifestations the marked involvement of several forms of deep sensibilities and the spontaneous pain on the anesthetic side constitute a separate group of sensory phenomena which are not encountered in cortical or capsular lesions. They are therefore pathognomonic of the thalamic syndrome originally described by Dejerine.

4. Edinger: Deutsch. Ztschr. f. Nervenhe., 1891, i, 262.

5. Roussy: Neurol. Rev., 1909, xvii, 301.

Sensory Disturbances from a Peduncular Lesion.—In Case 6 a tumor of the pituitary body disfigured the crura and all the elements in the posterior portions of the pons and medulla. The superficial sensations on the hemiplegic side presented a dissociation of a syringomyelic type with regard to touch and pain and also a thermic dissociation, the sense of cold being absent and extreme heat being taken for tepid. Among the deep sensibilities, the stereognostic sense was markedly impaired. Localization and pressure were but slightly involved. There was no crossed hemiplegia or crossed hemianesthesia. The cranial nerves were not invaded by the tumor. The pressure by the latter backward was such that it disfigured and displaced the crura and the pons, but did not completely destroy them. In this case we have, therefore, a conspicuous sensory symptom dissociation in the superficial sensibilities, with marked disturbances in the deep sensibilities. The latter were more pronounced than the former. The sensory disturbances were present on the side on which the motor function was impaired.

DIAGNOSTIC DEDUCTIONS

A review of the forms of impaired sensibility in various cerebral lesions demonstrates the fact that the superficial sensations are to a greater or lesser extent involved in all the lesions of the brain considered here. The capsular lesions give the most pronounced and the most persistent disturbances in the touch, pain and temperature senses. The least involvement is seen in the cortical cases. The three senses run parallel in degree and extent. A distinct dissociation is seen in the peduncular lesions and this dissociation is analogous to the syringomyelic type. In the thalamic cases there is also a dissociation, but of a special kind, namely, a diminution of touch sense, pleasant feeling from warmth and disagreeable feeling from cold. Disturbances in the deep sensibilities were found in all varieties of lesions considered here. The most constant and most extensive variety was the cortical one. Next in order of degree of involvement is the thalamic kind. Among all forms of deep sensibilities position and muscular sense were most frequently affected. These were disturbed in all except in the peduncular variety. The localization sense was found altered next in frequency. Astereognosis comes next in order of frequency.

In spite of this apparent regularity in sensory impairment, certain exceptions were nevertheless present. Special emphasis is laid on Case 3, in which an involvement of the parietal lobe and a destruction of the posterior portion of the internal capsule gave no sensory disturbances of any sort. In capsular lesions in which the superficial sensibility is so conspicuously involved there was also impairment of some deep sensibilities. In the peduncular variety the deep sensibilities were

more involved than the superficial ones. Astereognosis, which has been looked on as a symptom of a lesion in the parietal lobe, was present here, not only in the cortical, but also in the thalamic and peduncular, variety.

On the other hand, in Case 3 the lesion of the parietal lobe gave no disturbance of the stereognostic sense. Similarly, in the case reported by me⁶ in 1908 a bullet entered the left parietal region and subsequently an operation with extensive destruction in the same area did not cause a loss of the stereognostic sense or of any other form of sensations. Among other authors, Verger and Abadie,⁷ for example, published in 1900 the history of a case in which a sarcoma of the dura compressed the entire parietal lobe so that the cortex was markedly flattened and still the general sensibility and the stereognostic sense remained intact. In connection with these clinical irregularities, which are usually called exceptions, it may not be superfluous again to call attention to Case 7, in which a cortical hemorrhage strictly confined to the parietal lobe, but close to the ascending parietal convolution, gave place not only to an impairment of the superficial sensibilities, which was to be expected, but also to a motor hemiplegia, although the hemorrhagic area was far removed from the anterior central convolution.

The problem of sensibility of cerebral origin, as studied from a clinical standpoint but verified by means of anatomic material, establishes the existence of types of sensory disorders more or less distinct from each other. The nine anatomoclinical cases described here corroborate in a general way the findings of some authors, yet the exceptional features are sufficiently conspicuous to emphasize the fact that certain conservative reservations must always be made when diagnostic inferences present themselves. Literature is abundant with examples which militate against the generally adopted views. Exclusivism is a method which may be damaging to diagnostic investigations.

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6. Gordon, A.: *Med. Rec.*, New York, April 18, 1908, lxxiii, 648.

7. Verger and Abadie: *Bull. Soc. d'anat. de Bordeaux*, April 30, 1900, p. 347.

THE ACTION OF THE VARIOUS FEMALE REMEDIES ON THE EXCISED INTESTINE OF THE RABBIT*

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OMAHA

In a recent communication¹ was presented the pharmacologic action of the so-called female remedies on strips of the excised uterus of the guinea-pig. Many of them depressed the activity of the strips, but it was suggested that this effect might have been nothing more than an action on nonstriped muscle in general and that it was in no sense specific to the uterus muscle. To investigate this question experiments have been made on other forms of smooth muscle, namely, strips of intestine of the rabbit and the arteries of the kidneys of dogs. The results of this work show that these drugs, when active, do not act specifically on the uterus.

The experiments on the intestine were made in a similar manner to the experiments on the excised uterus of the guinea-pigs; a segment of the small intestine of the rabbit, about 2 or 3 cm. long, was attached to a muscle lever and immersed in a well-aerated bath of Tyrode solution and the contractions recorded. Contractions are usually started shortly after placing the strips in the bath and continue fairly uniformly for some time. After obtaining a suitable control tracing the drugs to be examined were added to the bath to make a concentration of 1 to 1,000 as a rule, but at times a 1 to 2,000 or 1 to 500 solution. The same fluidextracts of the drugs were used in this work as in the previous work on strips of the uterus.

The Experimental Results: The manifestation of the activity of the drugs was practically the same as on the strips of the uterus, namely, the chief function affected was the amplitude of the excursions and, secondarily, the rate and the tone. Further, the results of the action were practically identical with the results on the uterine strips. The drugs that depressed the excursions, and the degree of their action, were practically the same in each series. The single drug that put the strips of uterus into tonic contraction had a somewhat similar action on the intestinal segments. The inactive drugs, with but a single exception (*Chamaelirium luteum*), were the same in each series.

The following drugs lowered the amplitude of the excursion and,

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1. Pilcher, Burman and Delzell: THE ARCHIVES INT. MED., 1916, xviii, 557.

secondarily, decreased the rate and lessened the tone in some instances: Jamaica dogwood (*Ichthyomethia piscipula*, Fig. 1), pulsatilla (*Pulsatilla pratensis*), unicorn root (*Aletris farinosa*, Fig. 2), and figwort (*Scrophularia marylandica*) were the most active, and while there were occasional segments that were but slightly depressed by these drugs, the contractions of the majority of them were usually inhibited shortly after adding the drug to the bath. Lady's-slipper (*Cypripedium pubescens*) and valerian (*Valeriana officinalis*, Fig. 3) were somewhat less active, but the oil of valerian was depressant in dilutions of 1 to 100,000 (Fig. 4). Skullcap (*Scutellaria lateriflora*), wild yam (*Dioscorea villosa*), liferoot (*Senecio aureus*) and false unicorn root (*Chamaelirium luteum*) possessed a slight depressant action; false unicorn root at times was rather active and this is the only drug whose action differed from that on the uterus, on which it had no effect.

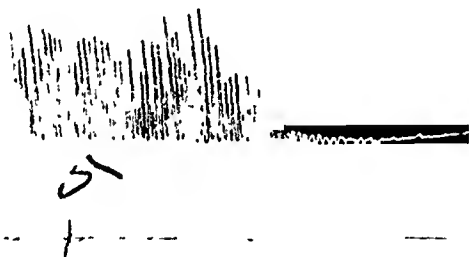


Fig. 1.—*Ichthyomethia piscipula* (Jamaica dogwood) on strip of rabbit intestine, applied at "5," to make a 1 to 1,000 solution.

Blue cohosh (*Caulophyllum thalictroides*, Fig. 5) inhibited the contractions and left the tone somewhat above the normal, but did not put the strips into tonic contraction as it did the strips of uterus.

The following drugs were practically void of action: blessed thistle (*Cnicus benedictus*), cramp bark (*Viburnum opulus*), black haw (*Viburnum prunifolium*), maple bark (*Acer spicatum*), passion flower (*Passiflora incarnata*), motherwort (*Leonurus cardiaca*) and squaw vine (*Mitchella repens*).

The Experimental Data: Pulsatilla was depressant in concentrations of 1 to 2,000 and the depression increased with the concentration. In two exceptional instances there was practically no effect with the 1 to 1,000 solution. In others the decrease in amplitude was quite marked. The rate was usually not altered appreciably. In all, sixteen experiments were made.

Aletris in the 1 to 1,000 solution usually stopped the contractions within a minute or two. Weaker solutions were also effective in the majority of cases.



Fig. 2.—Aletris farinosa (unicorn root) on strip of rabbit intestine, applied at "1," to make a 1 to 2,000 solution.



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Fig. 3.—Valerian on strip of rabbit intestine, applied at "1," to make a 1 to 1,000 solution.



Fig. 4.—Oil of valerian on strip of rabbit intestine, applied at "1," to make a 1 to 100,000 solution.



Fig. 5.—*Caulophyllum thalictroides* (blue cohosh) on strip of rabbit intestine, applied at "2," to make a 1 to 1,000 solution.

The tone was not lowered below the normal diastolic level. Fourteen experiments were made.

Ichthyomethia was used in but three experiments, as each time the concentrations ceased shortly after adding it to make a 1 to 1,000 concentration.

With *scrophularia*, in a large number of experiments, there was a uniform decrease in the amplitude of the excursion. The tone was frequently lowered, but the rate was not materially altered.

With *cypripedium* the amplitude was usually decreased with the 1 to 1,000 solution and constantly with the stronger ones. The action was less than with the drugs mentioned above.

Valerian was active in the concentration of 1 to 2,000 as well as with the 1 to 1,000. In five experiments with each dilution the amplitude was lessened in about one third of the experiments with a 1 to 100,000 solution, and more and the tone quite frequently lowered also. The oil of valerian was depressant frequently with the 1 to 50,000. Stronger solutions were not used, as it was the experience that strips of guinea-pig uterus did not recover from the depressant action of stronger solutions of oil.

Scutellaria and *Senecio aureus* were but slightly and inconstantly depressant with even the 1 to 500 solution.

Chamaelirium quite frequently lowered the amplitude of the excursions, but often was not effective. It is the only member of the series that exhibited a different action on the intestinal and uterine strips, for there was practically no action on the latter; however, the depression of the intestinal strips was not of sufficient degree to warrant attention.

Caulophyllum was quite active in depressing the amplitude of the excursions with the 1 to 2,000 solution, but had little action on the tone, differing in this respect from the action on the strips of uterus. On adding the drug the excursions were rather promptly lessened, but the tone remained just a little above the original diastolic level, whereas strips of the uterus were put into tonic contraction, frequently considerably above the previous maximal level.

The Inactive Drugs: As the drugs that were inactive on the uterus were inactive on the intestinal strips, but two or three experiments were made with each of them. In three of seven experiments with *Viburnum prunifolium* there was slight depression of the amplitude, but this was so insignificant and inconstant as to be deemed negligible.

The experiments on arteries: To test the effect of these drugs on the smooth muscle of arteries the kidneys of a number of dogs were perfused with concentrations of 1 to 500. As is well known, vasoconstricting drugs decrease the vein flow of perfused kidneys and vasodilators increase the flow. The kidneys were perfused with a 1 per cent. solution of sodium chlorid until the outflow was fairly constant, and then a 1 to 500 solution of a drug was substituted. The following drugs were examined in this manner and none of them materially altered the perfusion rate, indicating that there was no action on the vessels: unicorn root, Jamaica dogwood, pulsatilla, figwort and blue cohosh.

COMMENT

The results of this work indicate that the members of the group of female remedies that act on strips of uterus exhibit practically an identical action on strips of intestine, both in manner and degree of action. The other drugs of the group have no effect on either uterus or

intestine. This shows that they in no sense act specifically on the uterus. While there are no experiments on the effect of these drugs on the intact uterus and intestine, it is highly probable that doses that would influence the movements of the uterus would have the same effect on the intestinal movements. Any beneficial action they might exhibit on the uterus—but such action is not conceivable—would be offset by the effect on the intestines, such as cessation of peristalsis, or in the case of one of the drugs, by a tonic contraction of the intestines.

CONCLUSION

The drugs in the list known as female remedies exhibit practically the same action on the excised intestine of the rabbit as on the excised uterus of the guinea-pig, showing that their action is in no sense specific to the uterus.

The following depress the intestinal strips actively in the concentrations used: Jamaica dogwood, pulsatilla, unicorn root and figwort; while valerian (the oil is very depressant) and lady's-slipper are less active; and skullcap, wild yam, liferoot and false unicorn depress very slightly.

The following are practically devoid of action: blessed thistle, cramp bark, maple bark, black haw, passion flower, motherwort and squaw vine.

They have no effect on the smooth muscle of arteries in rather concentrated solutions.

A STUDY OF A CASE OF INTERMITTENT COMPLETE DISSOCIATION OF AURICLES AND VENTRICLES PRESENTING UNUSUAL FEATURES*

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In the case which we are about to report the following features will receive consideration: a conduction defect in the main stem and the right branch of bundle demonstrable at all periods of associated contraction of auricle and ventricle; transient periods of complete dissociation of auricle and ventricle, some of which were closely associated with digitalis administration; a rate of ventricle which exceeded that of the auricle in all periods of dissociation, except one; the occurrence of frequent junctional premature beats during periods of normal sequence of contraction; variations observed in ventricular complex; the apparent relation of digitalis administration with disturbances of mechanism as above noted, and with the degree of heart failure as estimated at a given time.

Case History.—F. W., aged 61, a real estate broker, was admitted to the St. Francis Hospital on Nov. 17, 1915. He was transferred to the medical service two days later, at which time his chief complaint was "asthma," a term which he applied to severe, acute attacks of breathlessness, accompanied by productive cough, wheezing and great physical and mental distress. These attacks were of brief duration. They had occurred with increasing frequency during the previous two years, and were more likely to occur at night. During the preceding year the patient had noticed a steadily decreasing field of effort. Thus, dyspnea on severe exertion later became dyspnea when the patient was at rest. There had been a coincident loss in weight, stated at about 25 pounds. During the three days previous to admission, the patient had received a total of 3 c.c. of tincture of digitalis. No history of previous digitalis administration could be elicited.

The past history was negative in regard to the members of the rheumatic group and to syphilis. The patient had used tobacco and alcohol, but both in moderation.

The physical examination on admission showed that the patient was in marked distress because of dyspnea of such grade as to require the constant use of a back rest. His color was pale, lips cyanotic; the venules were distended over the nose and the cheeks; the carotids were throbbing; there was marked pulsation of the jugulars; the apex was displaced downward and to the left. No gross arrhythmia was noted at this time, but the rate of pulse varied widely: thus, it was between 100 and 120 while the patient was free from his attacks of breathlessness. During such attacks the rate increased to 150. The palpable arteries were moderately sclerotic. The blood pressure was 140 systolic and 70 diastolic. The area of precordial dulness was increased, the right border

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* From the University of Pittsburgh, School of Medicine.

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of dulness being 4.5 cm. to right of the midsternal line at the fourth interspace, and the left border of dulness 14.5 cm., in the sixth interspace. There was no evidence of pericardial effusion. Mitral insufficiency was evidenced by the constant presence of a musical systolic murmur with the point of maximum intensity at the apex, and with transmission upward and to the left as far as the posterior axillary line, the second sound in pulmonary region being markedly accentuated. Edema of the lungs was present. There was marked subcutaneous edema over the sternum, sacrum and tibiae. The liver was enlarged and tender, the lower border extending 4 cm. below the costal margin in the midclavicular line.

An examination of the cardiac mechanism (Fig. 1) disclosed right bundle defect and an *As-Vs* interval of 0.3 of a second in Lead II. The urine was of low specific gravity, with a trace of albumin and a few hyaline and granular casts. The blood Wassermann reaction was negative.

Subsequent Course of Case.—The patient remained in the hospital twenty-eight days. During all of this period decompensation was marked, while at times it became acute and very alarming. Nevertheless, the mass movement of blood gradually improved under rest and symptomatic treatment. During the last few days in the hospital the patient became dissatisfied with his environment, and strongly objected to the taking of tracings and electrocardiograms.

Electrocardiographic records were made on six different occasions. In the first four of these records, made at intervals of three days during a period of twelve days following admission, association is shown (Figs. 1 and 2). The records made on December 13, twenty-six days after digitalis administration, show periods of complete dissociation (Fig. 4). Records made on the following day show normal sequence of chamber contraction.

On Dec. 16, 1915, the patient left the hospital against advice, and for a brief period was under the care of one of us. Subsequently, his family decided to remove him from medical treatment. Thereafter, all restriction of effort was apparently disregarded. The patient went up and down stairs several times daily, and took a number of rather long walks. Within a short time decompensation became grave, and the "asthmatic" attacks reappeared.

On Feb. 3, 1916, one of us was again called to see the patient at his home. He was found to be in a state of extreme agitation and exhaustion. Decompensation was profound, the evidence being orthopnea, a barely perceptible radial pulse, pulmonary edema, and general venous stasis. The lower border of the liver was demonstrable at the level of the umbilicus in the right midclavicular line. At this period digitalis administration was begun in the full realization of the possibility of the conduction defect being increased by its use. A total amount of 4 c.c. was given during a period of three days, and the patient was urged to return to the hospital that possible unfavorable digitalis effect might be promptly recognized. He was readmitted on February 6, and on both February 7 and 8 he received 2 c.c. of tincture of digitalis.

Venesection was performed on February 7, with temporary relief of stasis. On February 9 no digitalis was given. Electrocardiographic records made on February 8 and 9 (Fig. 5) showed complete dissociation. It is to be noted that at this period the patient had taken a total of 8 c.c. of tincture of digitalis. Early in the morning of February 10 venesection was again performed. On this day the patient's condition became so alarming that 0.4 mg. of strophanthin was given intravenously, and the patient was put on 4 c.c. of tincture of digitalis daily. Following strophanthin there was marked improvement of the patient's condition, both subjective and objective.

Electrocardiographic records (Fig. 6) made six and one-half hours after strophanthin injection showed a normal sequence of chamber contractions, but varying *P-R* intervals. On the following day, February 11, periods occurred of both normal sequence and complete dissociation. On the records showing normal sequence a great number of junctional premature beats is shown (Fig. 7). On Feb. 12, 1916, the digitalis was cut to 2 c.c. daily and continued

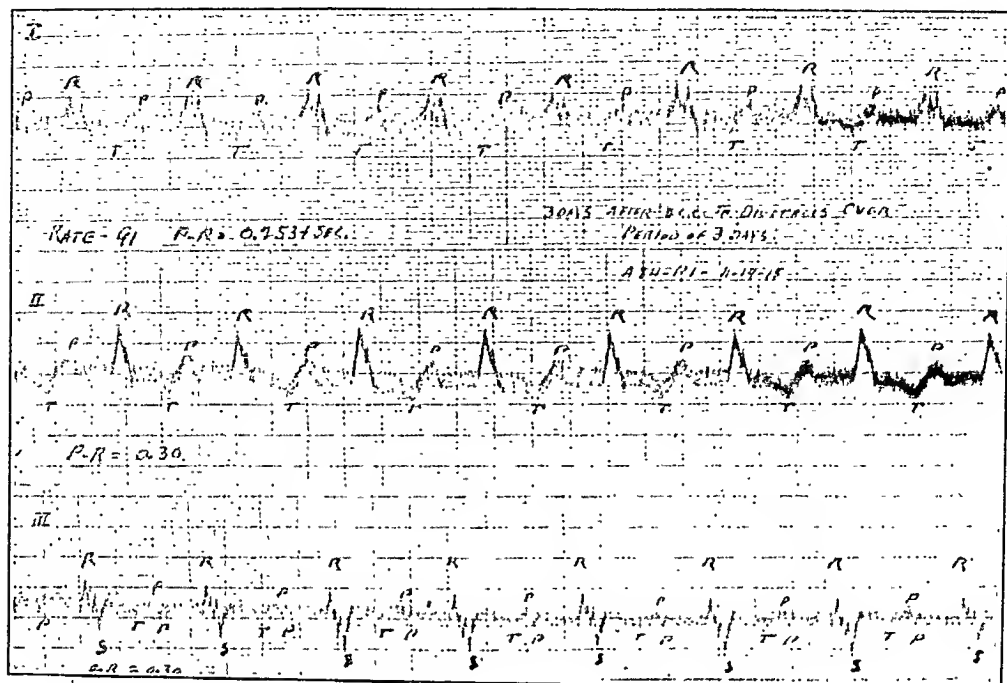


Fig. 1 (Plate 1).—Nov. 19, 1915. Right branch bundle defect and prolongation of *P-R* interval are shown. The heart is responding to impulses originating in the sino-auricular node. A condition of 2 to 1 block cannot be excluded in this electrocardiogram. This plate was taken three days after digitalis had been discontinued, the total amount ingested having been 3 c.c. of the tincture administered over a period of three consecutive days.

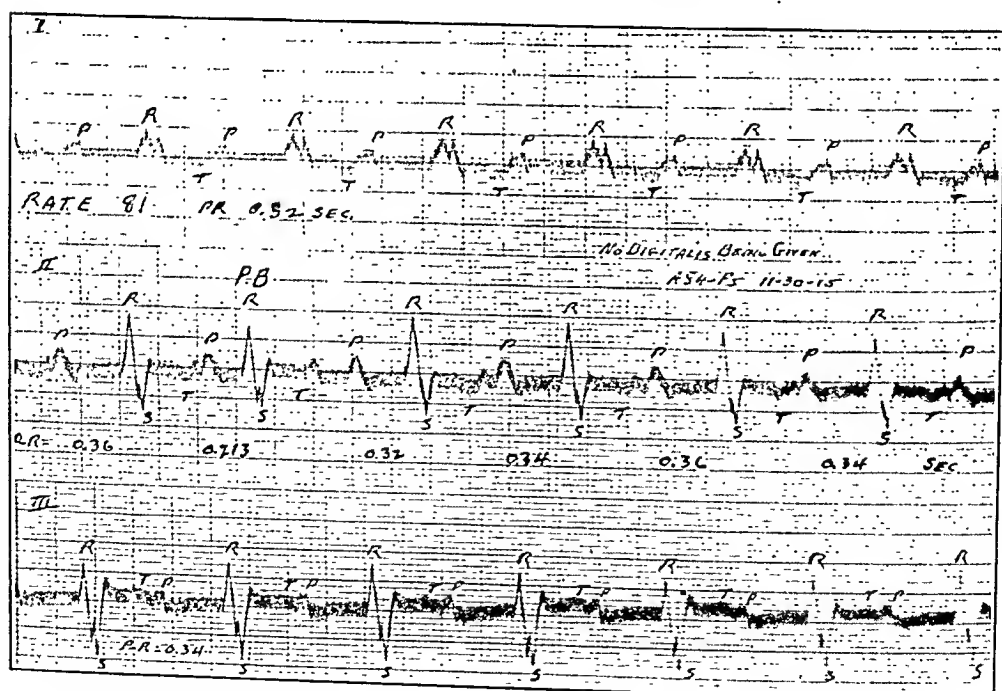


Fig. 2 (Plate 5).—Nov. 30, 1915. Right branch bundle defect, prolongation of *P-R* interval; sino-auricular rhythm; 2 to 1 block excluded by failure of curve to space for buried *P*, while furthermore, iso-electric line following junctional premature beat in Lead II is not broken by *P* complex.

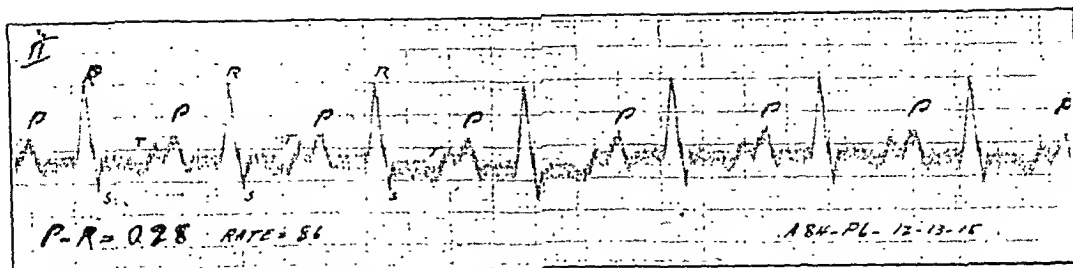


Fig. 3 (Plate 6).—Lead II. Dec. 13, 1915. Heart responded to impulses originated in sino-auricular node.

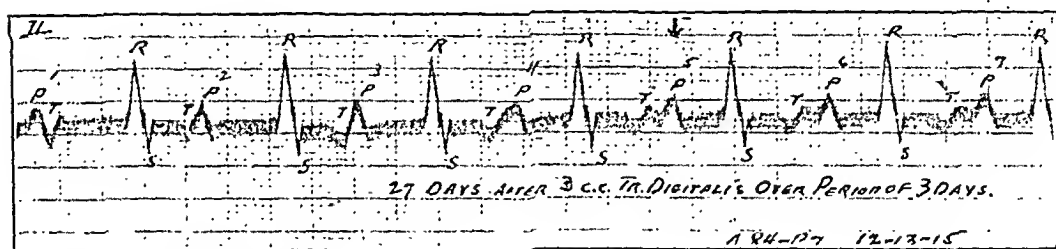


Fig. 4 (Plate 7).—Taken on same day as Figure 3. In Figure 3 the sino-auricular node is dominant for the whole heart. In this figure complete dissociation is shown over the first four cycles, after which the P-R interval remains constant.

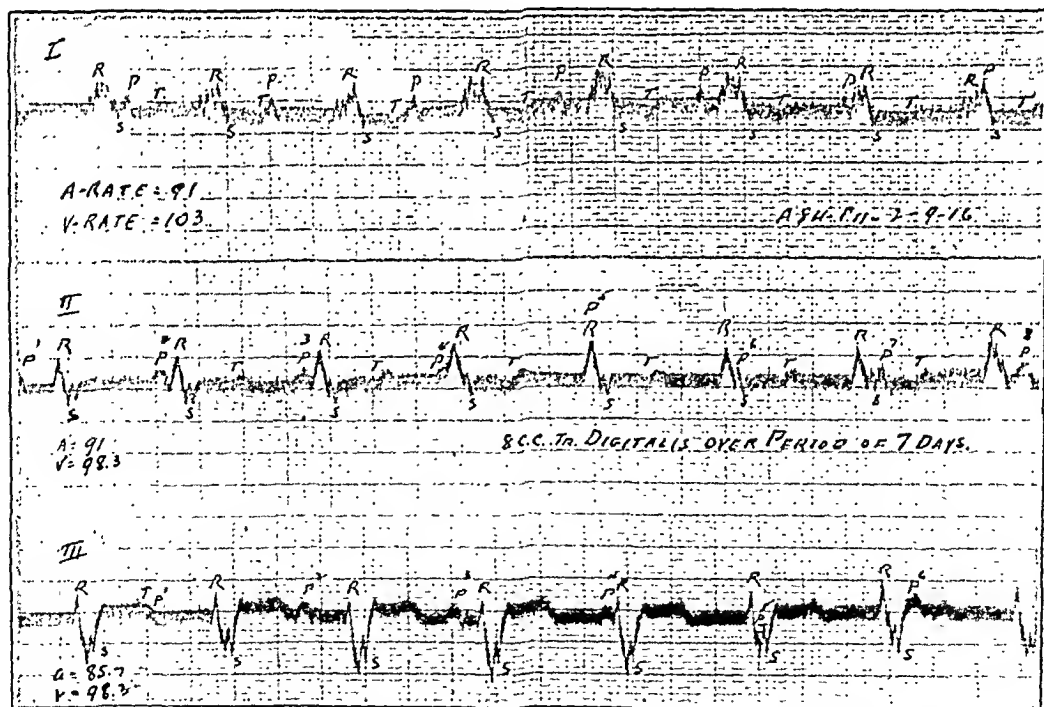


Fig. 5 (Plate 11).—Feb. 9, 1916. This plate was taken the third day after the second admission. The patient had taken 8 c.c. of tincture of digitalis over a period of seven days. Complete dissociation is shown; the ventricular rate is uniformly more rapid than the auricular. (A like mechanism is shown on a bromid strip made on the same day, over a period of forty-eight seconds.)

at this dosage until February 18, when it was entirely discontinued. On February 13, 14 and 15 electrocardiographic records (Fig. 8) showed complete dissociation; on February 16 the normal sequence of chamber contraction had been resumed (Fig. 9).

No digitalis was given from February 19 to March 3; but during this period there was a gradual rise of pulse rate, with an increasing deficit between fluid intake and output (Fig. 17). March 3 the condition of the patient was again very unsatisfactory. Cheyne-Stokes respiration was present even while the patient was awake. All electrocardiographic records made during this period had shown normal sequence of chamber contractions (Fig. 10). Nevertheless, in view of the urgency of the symptoms and of previous apparently favorable clinical results of digitalis administration, a further course of the remedy was now instituted. On March 4 the patient was given strophanthin, 0.4 mg. intravenously, and put on 4 c.c. tincture of digitalis daily. The digitalis was continued until the 13th, when it was cut to 2 c.c. daily and continued until the 19th. Electrocardiographic records made on the 10th, 11th, and 18th of

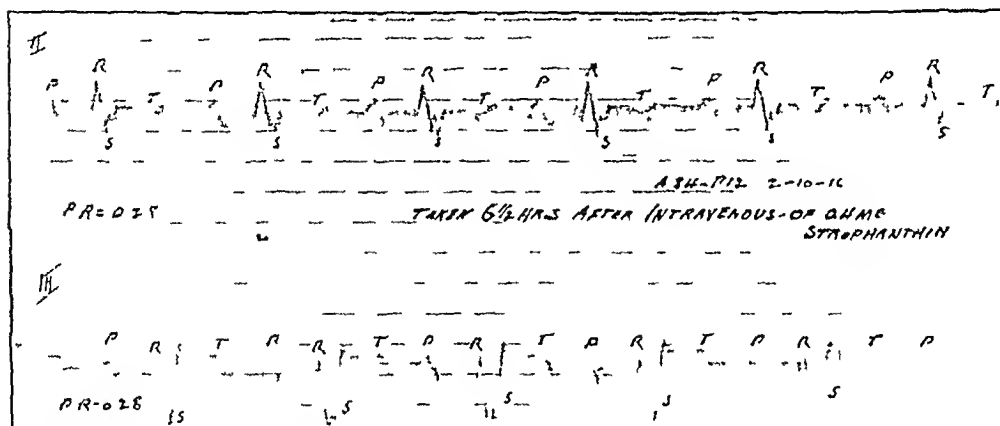
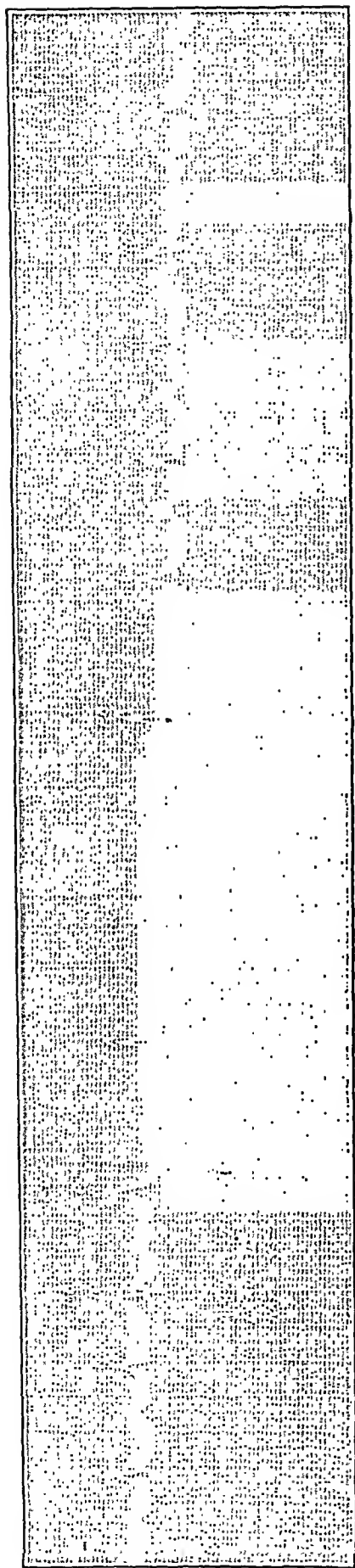


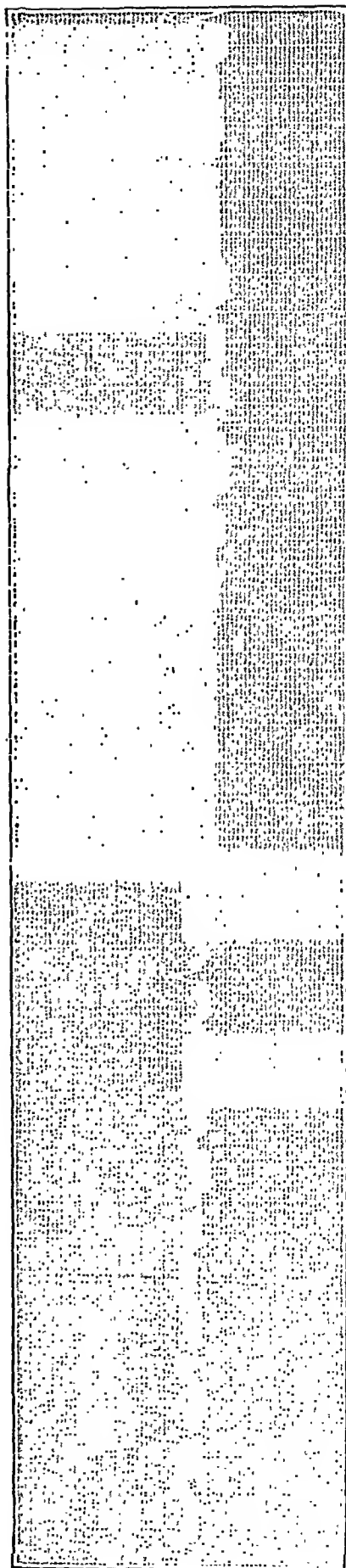
Fig. 6 (Plate 12).—Feb. 10, 1916. This plate was taken six and one-half hours after the intravenous injection of 0.4 mg. of strophanthin. There is apparent normal sequence of chamber contraction. Leads II and III are shown. The records made on the previous day (Fig. 5) had shown complete dissociation.

March showed complete dissociation (Fig. 11). This dissociation, unlike that exhibited earlier in the case, presented a ventricular rate somewhat below that of the auricles. From March 18 to March 22 the patient was given a prescription containing 0.2 gm. each of powdered digitalis, powdered squills and blue mass.

On March 23 he was again put on tincture of digitalis, 4 c.c. daily, and the foregoing prescription was discontinued. The last electrocardiographic records made on March 4 (Fig. 12) showed complete dissociation. During this second period of digitalis administration the fluid intake and output curves again approximated each other (Fig. 17), and there ensued marked improvement in the circulation. The subjective symptoms also abated to such a degree that on March 26 the patient insisted on leaving the hospital, stating that he was feeling too well to stay there. Heart failure was still marked at the time he passed from observation. We are informed he made a journey to and from Atlantic City in safety, but that he died seven weeks after his return. Unfortunately no records of cardiac mechanism were made after he left St. Francis Hospital, and necropsy was not obtained.



Part 1.



Part 2

Fig. 7 (Bromid Strip 5).—Feb. 11, 1916. Normal sino-auricular rhythm interrupted by frequent premature beats originating in junctional tissue.

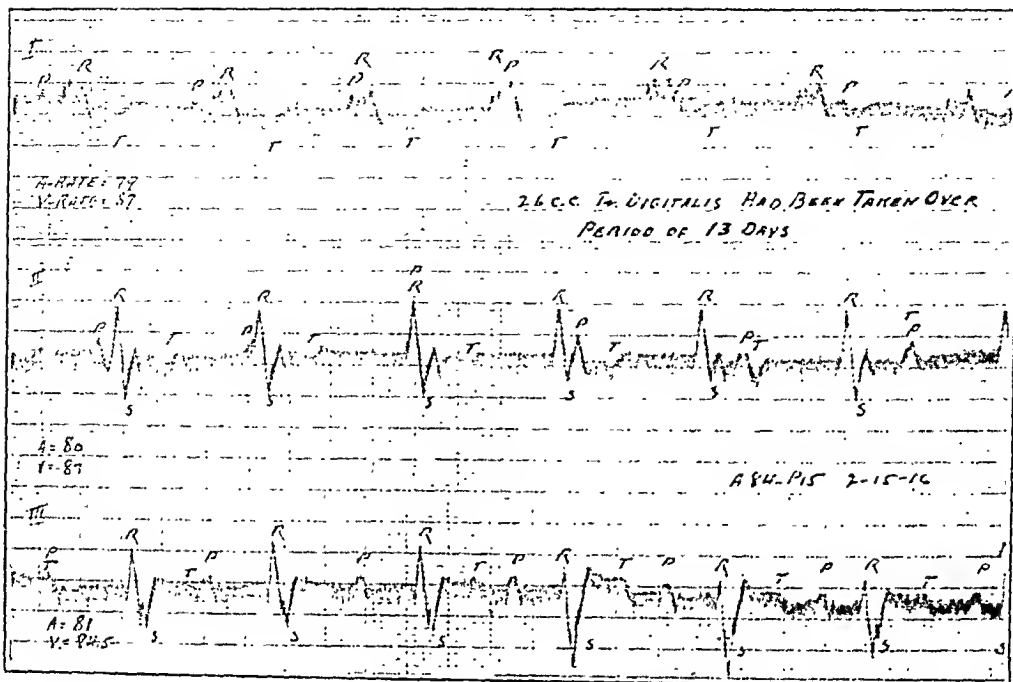


Fig. 8 (Plate 15).—Feb. 15, 1916. Complete dissociation, the ventricular rate being more rapid than the auricular. In Lead III the first three ventricular complexes suggest right preponderance; the three following complexes are suggestive of left preponderance, while the last R deflection appearing in this lead shows a tendency to return to contour noted in the first three complexes.

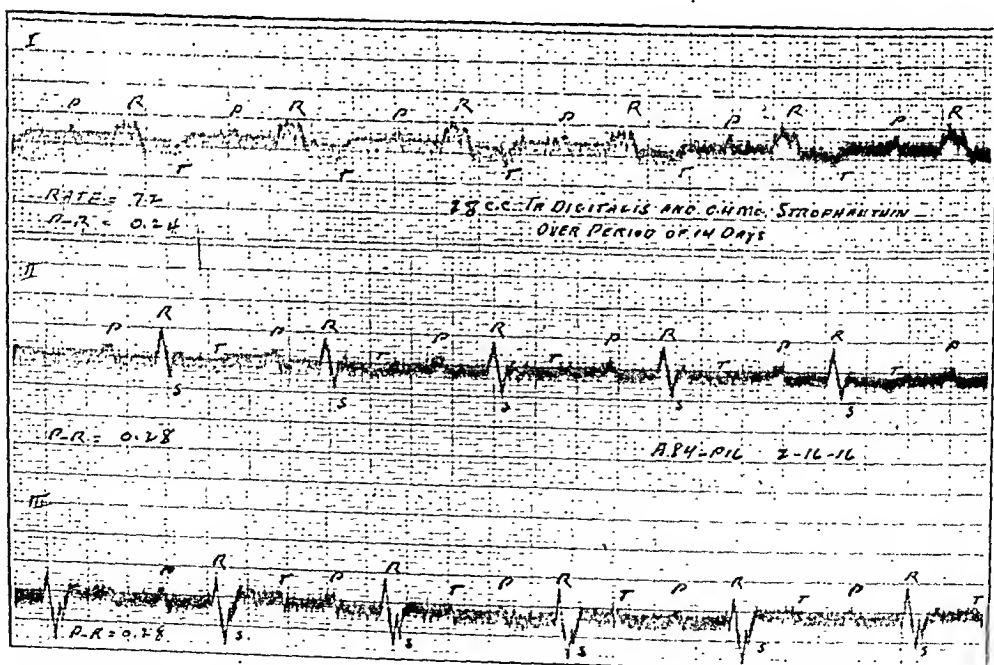


Fig. 9 (Plate 16).—Feb. 16, 1916. Normal sequence of chamber contractions is shown. A record made the day before (Fig. 8) shows complete dissociation. At this time the patient was being given tincture of digitalis, 2 c.c. daily.

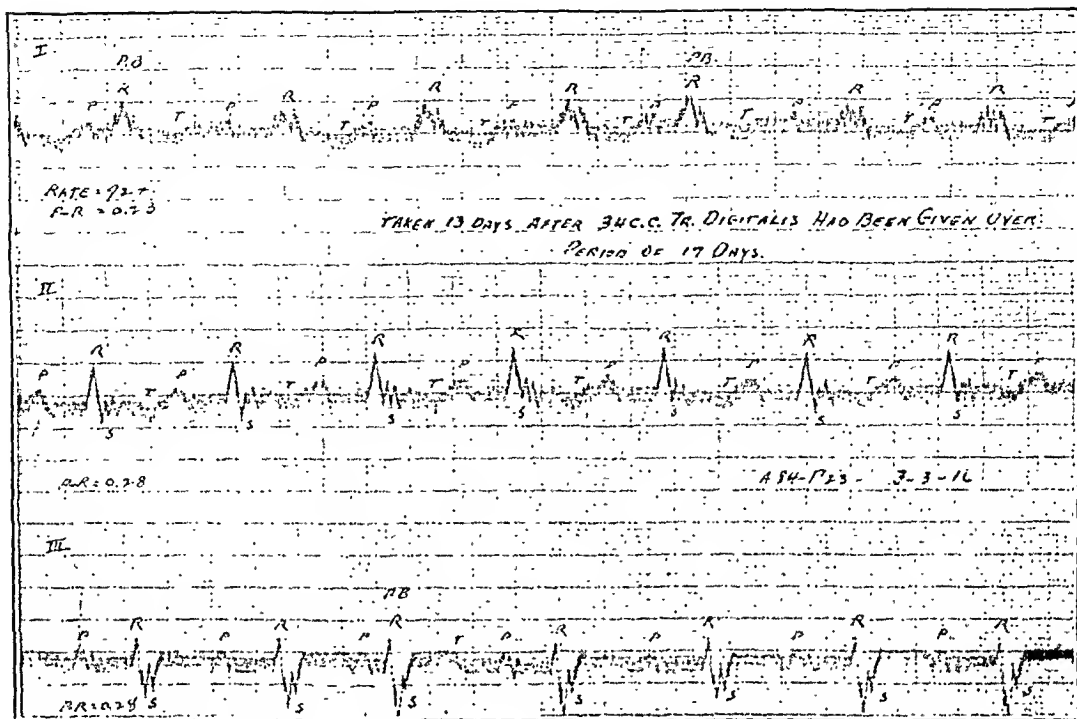


Fig. 10 (Plate 23).—March 3, 1916. Seven electrocardiograms taken since February 16 showed normal sequence of chamber contraction. No periods of dissociation were observed. The patient had had no digitalis for thirteen days. The clinical condition of the patient on this day was very unsatisfactory. Digitalis was resumed the following day. (See Figure 17.)

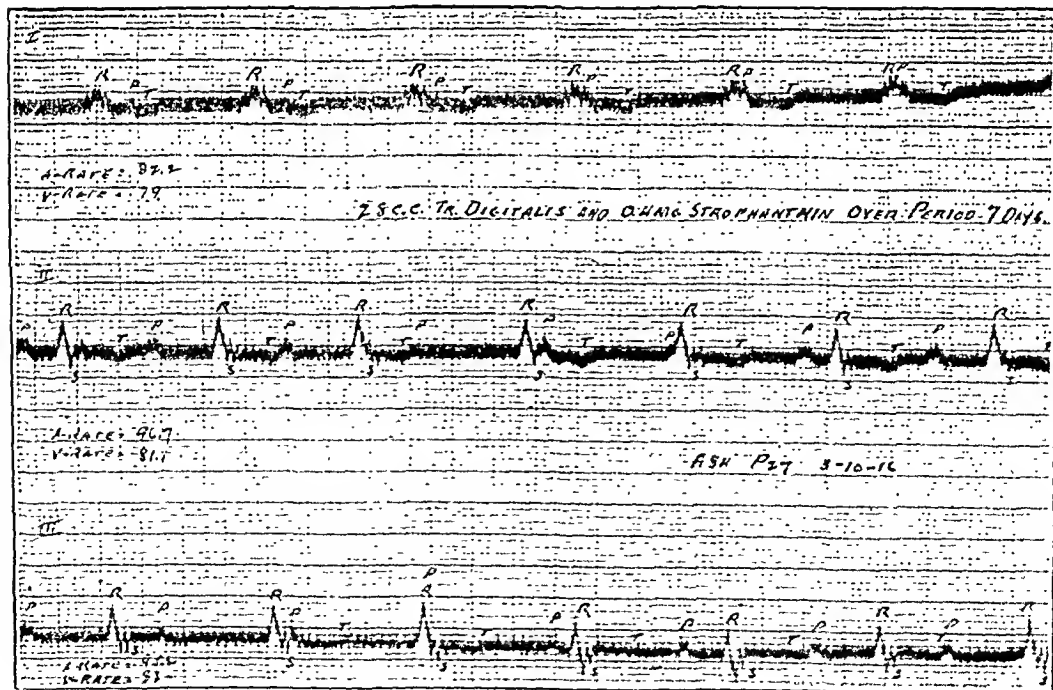
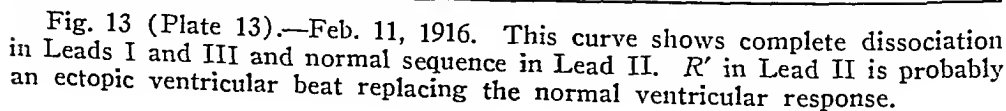
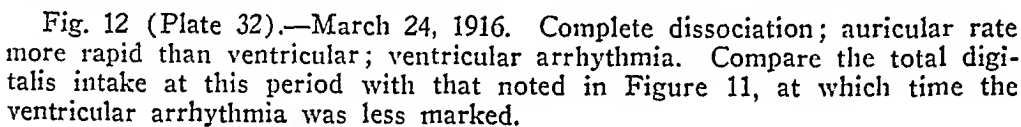


Fig. 11 (Plate 27).—March 10, 1916. It will be noted that the auricular rate is more rapid than the ventricular in all leads. The total digitalis intake at this period is indicated on the electrocardiogram.



COMMENT

Stem and branch bundle defect may be recognized in all curves showing association (Fig. 1). The question of 2 to 1 block cannot, we believe, be readily answered by a consideration of Figure 1 alone, since it is quite possible that a buried auricular complex may lie in the multiform *R-S* group. However, this difficulty disappears when we consider Figure 2, since the line following the junctional premature beat in Lead II would be broken by an auricular deflection if 2 to 1 block were present; nor will this figure space for 2 to 1 block. The close resemblance between the curves in the two figures is presumptive evidence that the mechanism in each instance is the same.

We believe that the conduction defects, evidenced by prolongation of *P-R* interval (Fig. 1) and by ventricular complexes indicating right branch bundle defect are due to permanent, obstructing lesions in the

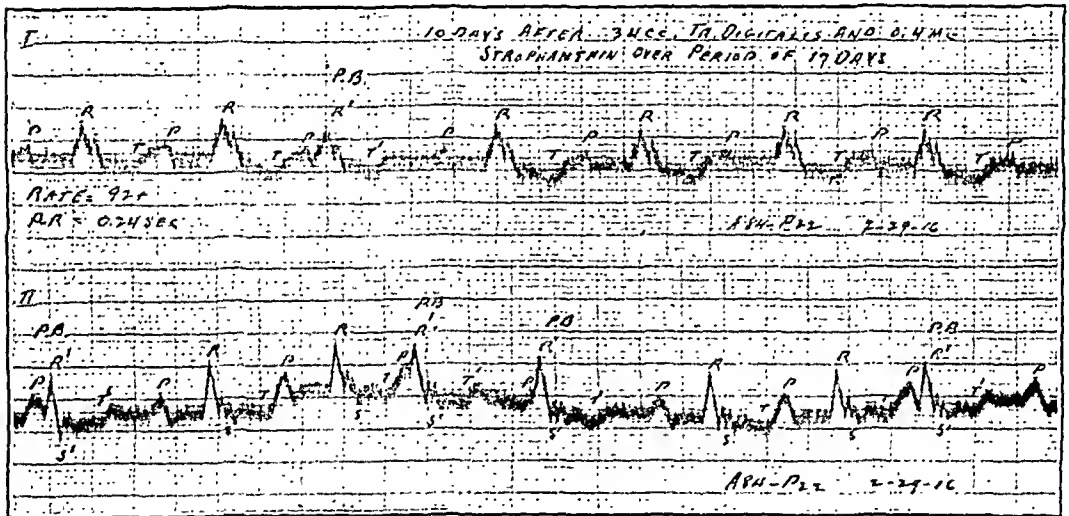
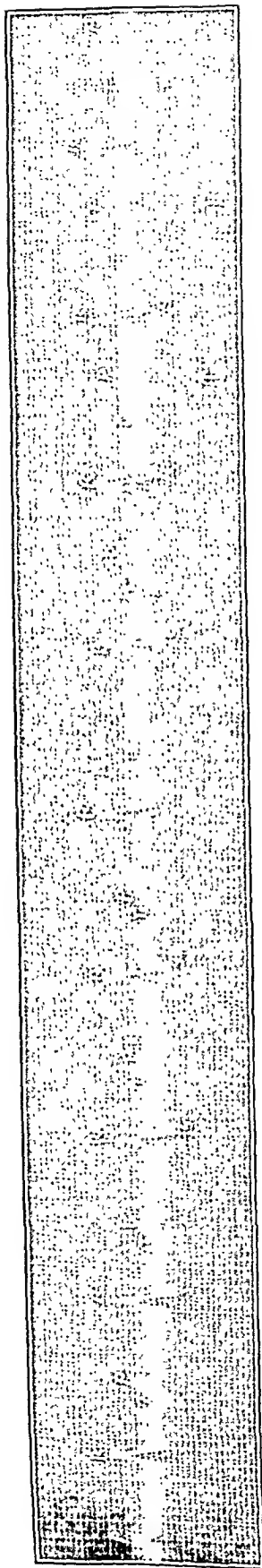


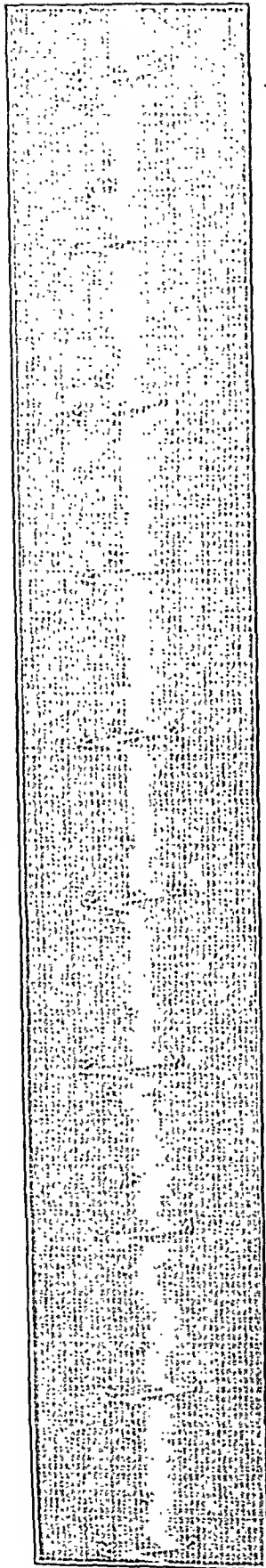
Fig. 14 (Plate 22).—Feb. 29, 1916. Leads I and II show frequent escape of junctional premature beat.

main stem of bundle and in its right branch, since, with minor variations, such defects remained constant during the entire period of observation. In the patient under consideration the etiology of these lesions is obscure. Not only were the usual laboratory tests for syphilis negative, but there was also no clinical or electrocardiographic change while the patient was being given specific treatment.

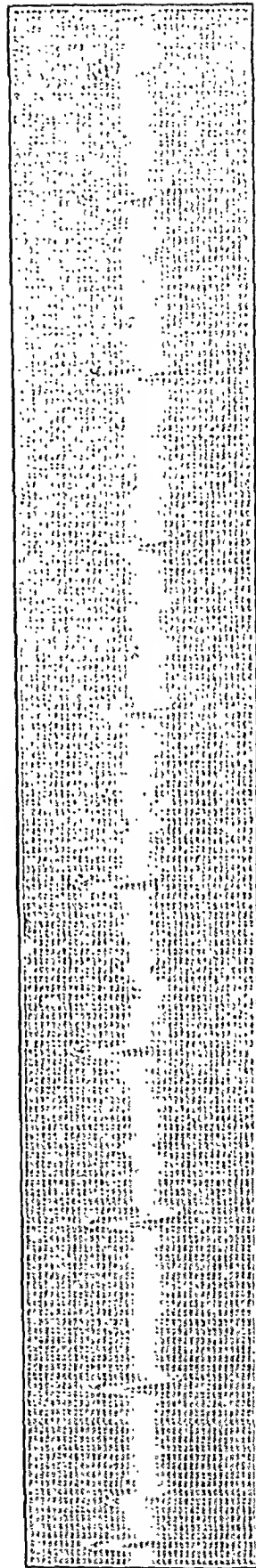
On the other hand, the periods of complete dissociation (Figs. 4, 5, 8, 11, 12) were transient. In our curves it may be shown that periods of complete dissociation alternated with periods of association (Figs. 4 and 13), and that at times both rhythms appear on a single electrocardiogram (Fig. 13). The cause of dissociation, therefore, must have been either intermittent in action or varying in intensity. The fact that conduction defects, amounting even to complete disso-



Part 1



Part 2



Part 3

Fig. 15 (Bromid Strip 6).—Feb. 13, 1916. Lead II; V rate 83.3; complete dissociation with apparent resumption of control of both chambers of the heart by the sinus node over two periods of two cycles each (indicated by arrows). P - R interval during what appears to be sino-auricular rhythm is 0.28 of a second. A study of many curves shows that this is the usual time interval during periods of association in this case.

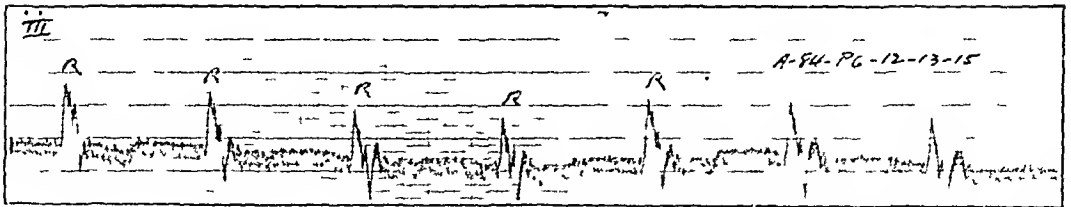


Fig. 16 (Plate 6).—Dec. 13, 1915. Type of ventricular complexes seen in Lead III suggesting right preponderance.

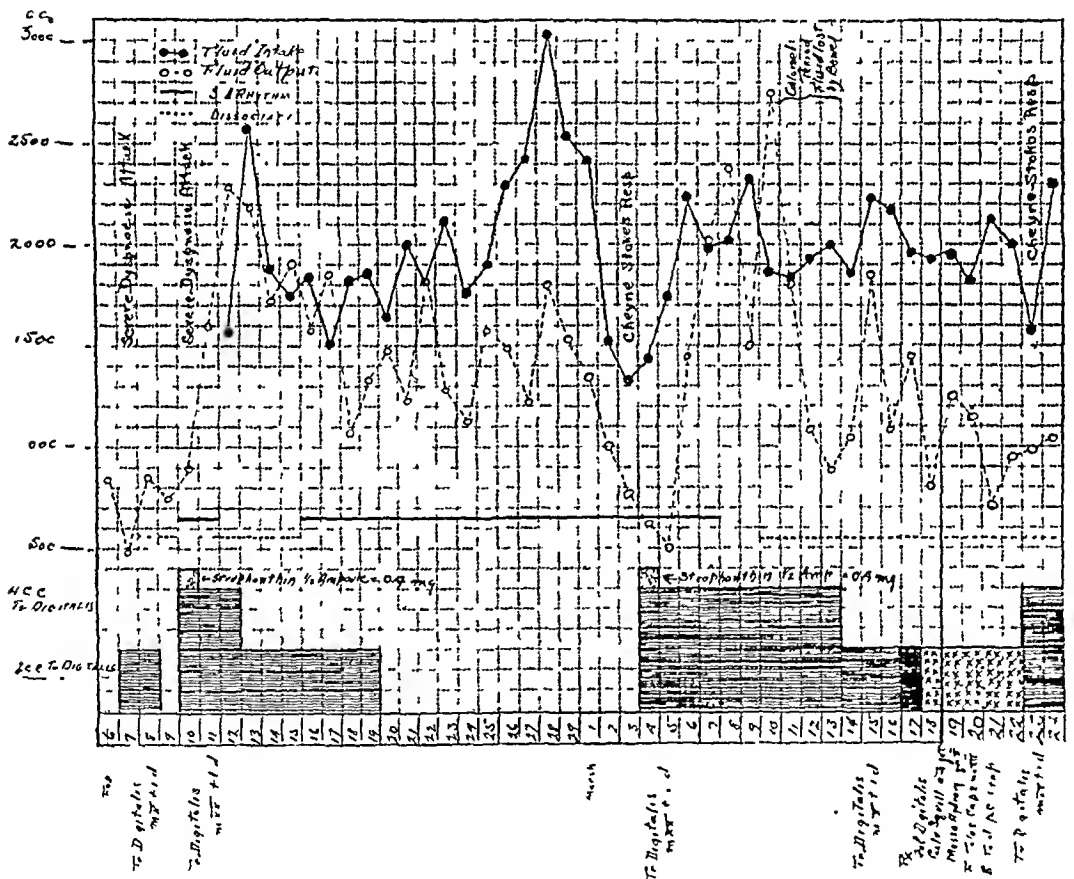


Fig. 17.—The irregular solid line indicates the fluid intake. The irregular dotted line indicates the fluid output. The solid straight line indicates the periods of sino-auricular rhythm. The dotted straight line shows the periods of complete dissociation. The various digitalis preparations administered are indicated by the blocks at the bottom of the chart. The marked decrease in fluid output on March 12, 13 and 14 is associated with the period of free catharsis.

ciation, may arise as a result of disturbance of function and in the absence of permanent obstructive lesions of the bundle we believe to be now well established. Proof of this is based on experimental and clinical evidence. Thus, Lewis, White and Meakins¹ have been able to produce functional heart block in the cat by means of asphyxia. This effect was observed when the heart was responding to sino-auricular rhythm, resulting in forward heart block, or when responding to atrioventricular rhythm, resulting in reversed or backward heart block. Such functional block, it was found, might be produced, intensified and usually relieved at will by regulating the degree of asphyxia to which the tissues were subjected.

Transient complete dissociation may be produced in the mammalian heart by the administration of digitalis. This type of dissociation is often characterized by a ventricular rate which may equal or even exceed the auricular rate. Cushny² notes this condition as a manifestation of frequent occurrence in the dog's heart in a toxic state of digitalization. Hewlett and Barringer,³ writing in 1909, state that the demonstration of this phenomenon is routine in the departments of physiology of Cornell University and of the University of Michigan. As to clinical evidence, not only do they instance a case occurring in the human subject, but Christian,⁴ writing in September, 1915, reports two cases (Cases 1 and 2) of transient auriculoventricular dissociation, associated with the administration of digitalis. In Case 1 of this series dissociation appeared after a period of administration of digitalis, disappeared during the period when the drug was discontinued, and reappeared when it was resumed. "At necropsy the heart showed no evident lesion of the conducting system, and during life blocking had been transitory."

Wilson⁵ has shown that in the experimental production of atrioventricular rhythm (of types with *P-R* interval of zero or an *R-P* interval) in the human subject under the influence of atropin, a variable period of dissociation occurs during the transition from normal sino-auricular rhythm to the induced atrioventricular rhythm, during which the auricles respond to impulses elaborated in the sino-auricular node and the ventricles to impulses generated in the *A-V* node.

1. Lewis, T., White, P. D., and Meakins, John: The Susceptible Region in *A-V* Conduction, *Heart*, 1914, v, 289.

2. Cushny, A. R.: Action of Digitalis Series on Circulation in Mammals, *Jour. Exper. Med.*, 1897, ii, 281.

3. Hewlett, A. W., and Barringer, T. B.: The Effect of Digitalis on the Ventricular Rate in Man, *THE ARCHIVES INT. MED.*, 1910, v, 93.

4. Christian, H. A.: Transient Auriculoventricular Dissociation with Varying Ventricular Complexes Caused by Digitalis, *THE ARCHIVES INT. MED.*, 1915, xvi, 341.

5. Wilson, F. N.: Regular Ectopic Rhythms, *Jour. Lab. and Clin. Med.*, 1916, i, 481.

Although this condition may not be regarded as a functional heart block in the strict interpretation of the term, it is, nevertheless, an instance in which, for transient periods of greater or less duration, there is an independent activity of auricles and ventricles. Lewis, White and Meakins mention epinephrin and anaphylaxis as causative agents in the production of transient complete heart block. It is also occasionally a complication or sequela of the various infections. It is to be observed that the above factors are all transitory in action and that the dissociation which they induce is not permanent.

The relatively rapid rate of the ventricles (Figs. 5 to 8) in our dissociation curves is of especial interest in view of the rarity of such finding in the reported cases of complete dissociation. It is a well-established fact that the rate of impulse formation of experimental bundle lesions is about 30. This is the rate of homogenetic impulse formation in centers below the seat of such lesions, and is the rate of ventricles observed in the majority of cases of clinical dissociation. However, the ventricles may respond to impulses which are furnished by centers having a higher rate of stimulus production than those in the lower portions of the conducting tissues. It has been shown that the automatic rate in ventricular rhythms under the control of the *A-V* node, while lower than that in which the rate is inaugurated by the sino-auricular node, is, nevertheless, higher than the rate in the usual clinical complete heart block, where the centers which lie at the lower levels of the conducting tissue are in control. But in our case the rate of the ventricle is always in excess of the rate of the auricle during the earlier period of observation (Figs. 5 to 8). Presupposing that this rate of ventricle is governed by *A-V* node, or junctional tissues, while the auricle is paced by the sino-auricular node, we find ourselves under the necessity of accounting for this inverted ratio of frequency in impulse formation between the two automatic centers. The solution is suggested by White,⁶ who says that "a rapid rhythm arising in atrioventricular junctional tissues, as in some cases of paroxysmal tachycardia, is possibly due to irritation, and not to normal rate of stimulus production in this area of the heart." With this opinion we agree, believing that in this manner, and because of the high location in *A-V* conducting tissues of the site of impulse formation, the rapid ventricular rhythm is produced. We are strengthened in this belief by the proof afforded by our own curves of the exhibition of a high degree of automaticity in these centers. This is evidenced by the frequent escape of premature contractions of junctional origin (Figs. 7 and 14) at a time when the ventricles were otherwise under domination by the sino-auricular node. Such increase in automaticity.

6. White, P. D.: THE ARCHIVES INT. MED., 1915, xvi, 518.

if the stimulus production is at a rate in excess of that of physiologic stimulus production or approximating it, we believe, may result in the shifting of the function of pacemaker for the ventricles from the sino-auricular node to some portion of the junctional tissue or the *A-V* node, while the auricles continue to respond to impulses originated at the normal site.

We believe that our dissociation curves are illustrative of such mechanism and that two pacemakers coexist, each of which is dominant for the chambers with which it is in closest physiologic connection. The auricles respond to impulses elaborated at approximately the normal rate in the sino-auricular node, and the ventricles to impulses originated at some point high in the *A-V* conducting tissues, which possess a relatively high rate of automaticity.

In addition, it was observed in three instances on our dissociation curves, where the time relationship of *P* and *R* approximated the normal (in this case 0.28 of a second in Lead II), that the sino-auricular rhythm appeared to become temporarily dominant for the whole heart for a period of two complete cycles (Figs. 4 and 15). During the latter period of the study of this case, while the patient was under rather intensive digitalis therapy, the auricular rate was uniformly higher than the ventricular (Figs. 11 and 12), the rates gradually diverging toward the end of the time of our observation. Several factors are probably concerned in the production of this change. It is probably, in part, a manifestation of the usual effect of digitalis. (It is interesting to observe that whenever the effect of this drug became obvious it appeared to have been more pronounced in its action on the ventricular than on the auricular rate.) We must also bear in mind that the patient had undergone a long rest in bed, a fact which may have had something to do with permitting the subsidence of the irritation which we believe to have been present in *A-V* conduction tissues. Finally, it is possible that there had occurred a shifting of pacemaker to a lower level of conducting tissues, with a resulting rate more closely approaching that of ordinary idioventricular rhythm. On no occasion after the establishment of a ventricular rhythm slower than that of the auricle do our records show any evidence of the return of the heart to the sino-auricular rhythm, shown during periods when ventricular rate actually exceeded that of auricular. It would appear that with the divergence of rhythmicity of the two pacemakers there was a decreasing tendency for the sinus node to resume its physiologic function for the whole heart.

Form of Ventricular Complexes.—On several occasions in recent literature there have been references to variations in the form of ventricular complex. Such changes, in general, have been modifications

of ventricular form suggesting preponderant action of one side of the heart over that of the other. Cohn⁷ and others⁴ suggest that these variations arise as a result of temporary impassability of the conducting tissues, first of one part and then of another. It is thought that such impassability may arise in some instances as a result of the action of digitalis or of other toxic agents.

In our case the changes in contour of ventricular complexes occurred both while the patient was definitely under the influence of digitalis and also at times when such influence was not apparent. These changes occurred while the heart was responding to sino-auricular rhythm and also during periods of complete dissociation. They were most marked in the ventricular complexes of Leads II and III. The usual complex suggested the type associated with left preponderance (Figs. 1 to 5). On some days the contour of ventricular complexes, especially in Lead III, was of the type associated with right preponderance (Fig. 16). At other times there were isolated or grouped instances of alteration from one form to the other in the same lead (Fig. 8). Many changes of form intermediate between them were observed.

Digitalis effects, as expressed by alteration in contour of *T* wave,⁸ or in prolongation of *P-R* interval,⁹ were not apparent in our case, though a series of about thirty electrocardiograms taken during digitalis administration was examined for such changes. We have no doubt that this is because the reaction of a definitely damaged heart to this drug can scarcely be compared with the reaction of apparently normal hearts. During the last period of digitalis therapy a marked ventricular arrhythmia (Fig. 12) occurred at a time when the heart was in dissociation. We believe this to be a manifestation of the action of digitalis.²

The clinical results of digitalis therapy in regard to this patient were always favorable, sometimes strikingly so. The effect on fluid output is shown in Figure 17, for which we are indebted to Dr. J. C. Baldwin. In the period of discontinuance of digitalis, during the mid-period of second admission, heart failure became progressively more marked; the resumption of digitalis was followed by a correspondingly marked improvement in the circulation. This observation is of especial

7. Cohn, A. E.: The Present Status of the Electrocardiographic Method in Clinical Medicine, *Am. Jour. Med. Sc.*, 1916, cli, 541; A Case of Transient Complete Auriculoventricular Dissociation, showing Constantly Varying Ventricular Complexes, *Heart*, 1913, v, 5.

8. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Effect of Digitalis on the *T* Wave of the Normal Human Electrocardiogram, *Jour. Exper. Med.*, 1915, xxi, 593.

9. White, P. D., and Sattler, R. R.: The Effect of Digitalis on the Normal Human Electrocardiogram, with Especial Reference to *A-V* Conduction, *Jour. Exper. Med.*, 1916, xxiii, 613.

interest in view of the existence of a distinct theoretical contraindication for the use of digitalis in this case. A record of the digitalis administration during the entire period of observation is shown in the table.

TABLE OF DIGITALIS AND ALLIED DRUGS ADMINISTERED

Date 11/13/15	Preparation Tr. Digitalis	Daily Doses 1 c.c.	Total Doses 3 c.c.
First admission			
11/16/15	None		
11/16/15 to 2/2 16	None		
2/ 3/16	Tr. Digitalis	1 c.c.	
2/ 4/16	Tr. Digitalis	2.33 c.c.	
2/ 5/16	Tr. Digitalis	0.67 c.c.	4 c.c.
Second admission	None		
2/ 7/16	Tr. Digitalis	2 c.c.	
2/ 8/16	Tr. Digitalis	2 c.c.	4 c.c.
2/10/16	Strophanthin (intravenous)	0.4 mg.	0.4 mg.
2/10-13/16	Tr. Digitalis	4 c.c.	12 c.c.
2/13-19/16	Tr. Digitalis	2 c.c.	14 c.c.
3/3/16	Strophanthin (intravenous)	0.4 mg.	0.4 mg.
3/ 3-14/16	Tr. Digitalis	4 c.c.	40 c.c.
3/14-18/16	Tr. Digitalis	2 c.c.	8 c.c.
3/18-22/16	Pow'd digitalis	0.2 gm.	1 gm.
	Powdered squills	0.2 gm.	1 gm.
3/23-25/16	Tr. Digitalis	4 c.c.	12 c.c.

SUMMARY

A case is reported in which a sino-auricular rhythm of the whole heart is interrupted by periods of total dissociation of auricles and ventricles. During all but one of these periods the rate of the ventricles exceeded that of the auricles. This type of rhythm is highly suggestive of digitalis poisoning. It is admitted that digitalis effect could not have been absolutely excluded at any time while our patient remained under observation. Nevertheless, because we take into account the fact that the first onset of dissociation was observed twenty-eight days after the ingestion of 3 c.c. of tincture of digitalis, extending over a period of three days, we believe that the connection between the administration of digitalis and dissociation is problematic. On the other hand, a positive effect of digitalis administration may be noted in the marked clinical improvement which occurred more than once in a patient in whom stem and branch bundle defect would have been regarded under ordinary circumstances as a contraindication to the use of the drug.

EXPERIMENTS ON THE ORIGIN AND CONDUCTION OF THE CARDIAC IMPULSE

VI. CONDUCTION OF THE EXCITATION FROM THE SINO-AURICULAR NODE TO THE RIGHT AURICLE AND AURICULOVENTRICULAR NODE *

J. A. E. EYSTER, M.D., AND WALTER J. MEEK, PH.D.

INTRODUCTION

The experiments to be described in this paper were undertaken in an attempt to determine the normal path or paths of conduction of the cardiac impulse from its origin in the upper part of the sino-auricular node to the right auricle and to the auriculoventricular node. The problem was attacked in two ways: first, by an attempt to map out the path of the spread of electronegativity from the sino-auricular node to surrounding parts in the intact heart; and second, the determination of the influence on conduction from the sino-auricular node to the right auricle and auriculoventricular node produced by a gradual and progressive isolation of the sino-auricular node from the surrounding tissues.

So far as we have been able to find, no previous work has been done in which the sino-auricular node has been gradually isolated from the surrounding tissues in the heart in situ, with the exception of a few experiments of this character reported by us in a preceding paper of this series.¹ Cohn, Kessel and Mason,² working on the excised artificially perfused dog's heart, state that such incisions cause merely an increase in rate of the heart. Hering³ found that a single cut through the sulcus terminalis may cause a transitory stoppage of the supraventricular regions, a result not confirmed by subsequent workers.

METHODS

The experiments were all performed on dogs. The animals were given a preliminary injection of morphin, etherized and the thorax opened under artificial respiration with air warmed to body temperature. An extensive exposure of the right auricle and intercaval regions was obtained by opening the thorax well down on the right side and rotating the heart slightly to the left, in which position it was held by

* Submitted for publication July 11, 1916.

* From the Physiological Laboratory of the University of Wisconsin.

1. Meek and Eyster: *Heart*, 1914, v, 227.

2. Cohn, Kessel and Mason: *Heart*, 1911-1912, iii, 311, 341.

3. Hering: *Arch. f. d. ges. Physiol.*, 1910, cxxxvi, 466.

ligatures attached to the auriculoventricular border. Systoles of the right auricle and right ventricle were recorded by suspension and air transmission to ambours writing on a Hürthle kymographion or recording on bromid paper in a photographic registration apparatus. In addition, galvanometric records of one type or another were made in all experiments except four (Experiments 11, 12, 15 and 16). The large electromagnetic thread galvanometer of Edelmann was used for this purpose. These records were made always for one of two purposes, either to determine the seat of the pacemaker and to trace the course of the wave of negativity by determining the sequence of negativity at certain selected points, or to determine the time relation of onset of negativity in any two or more points. The first method depends on the fact that if the direction of movement of the galvanometer fiber, when one of the terminals becomes electronegative to the other, is determined beforehand, it is possible to find which one of any two points shows the initial change in this respect. By selecting a number of points on the surface of the heart it is possible by comparing each one of these with every other one to determine the sequence of negativity in these various regions. For reasons which we have previously discussed,⁴ we do not regard this method, however, as suitable for the accurate determination of the time intervals of the occurrence of negativity in different regions. To determine this we have used two other methods, the first of which we have already described.⁴ This consists in a determination of the difference in time between the occurrence of the initial electrical change at any two points and the onset of mechanical systole of the auricle as recorded by the suspension curve. If the negativity in point *a* precedes the mechanical systole by an interval of time represented by *x*, and point *b* by an interval of time represented by *y*, the time from the appearance of negativity in *a* to that in *b* would be given by $x - y$. This method of measuring the rate of propagation was used in five experiments reported in this paper (Experiments 32 to 36, inclusive). There are two disadvantages connected with this method: first, the difficulty of determining on a record taken at fast speed, when dealing with small intervals of time, the exact onset of the mechanical systole; and second, the fact that determinations are not made within the same heart beat, but involve comparisons between different cycles. The latter we minimized by devising a key which allowed rapid change of connections, so that comparisons between the galvanometer curves from a number of different points and the suspension curve could be made over a minimal number of heart cycles. The second method for determining the time interval of negativity between two points consists in using two

4. Eyster and Meek: *Heart*, 1914, v, 119.

separate circuits to two galvanometers, a pair of electrodes placed close together⁵ being applied to each region and connected to one of the galvanometers, the other point carrying two electrodes connected similarly to the other galvanometer. The difference in time of onset of the two curves is a measure of the time relation of the onset of the electrical change in the two regions. The records in all cases were made on bromid paper moving usually at a speed such that the marks of a tuning fork vibrating 100 times per second were spaced from 2 to 4 mm. apart. Since the onset of such curves is nearly always very sharp, accurate time measurements with an error less than 0.0025 of a second were possible.

The electrodes used were of the zinc and zinc sulphate type. When applied to the surface of the heart, the terminal was composed of a piece of woolen yarn saturated with salt solution and attached to the epicardium with a light silk ligature. For application to the auricular portion of the auriculoventricular node (coronary sinus⁶) a curved electrode terminating in a soft pad of macerated filter paper, was applied to the region of the mouth of the coronary vein on the external surface of the auricle. For application to the ventricular portion of the auriculoventricular node, a similar electrode, but longer and curved near the tip, was passed down through the right external jugular vein and superior vena cava until its end was in contact with the interauricular septum in the region over the node. The position of this electrode was confirmed by examination after the experiment was terminated. When two galvanometers were used for determining the time interval of the electrical change, a pair of electrodes cemented together were applied as above.

In those experiments in which the region of the sino-auricular node was gradually isolated and the influence on the seat of impulse formation and on conduction studied, interruption of the physiologic continuity of the tissues was secured by ligating, clamping, or cutting. Ligation was only employed when the span of tissue included was short and serious distortion of neighboring parts was not produced. In all cases in which the extent of the region to be interrupted was greater, clamping or cutting was employed. When it was desired that the interruption be permanent, the tissue was cut. Clamping, on the other hand, was resorted to when the results of gradual or temporary interruption of the functional continuity were desired. The clamp used was

5. We here found this more satisfactory in practice than the employment of the so-called differential electrode of Clements (*Ztschr.*, 1912, lviii, 110). In this a single bent thread connected with two electrodes is applied to the heart. The decrease in the electrical potential difference by this procedure may tend to cause the loss of a small initial change and the comparative looseness of the galvanometer fiber required results in slower reactivity.

6. Aschoff: *Centralbl. f. allg. Path. u path. Anat.*, 1910, xxi, 433.

one devised for the purpose and consisted of a holder through which a straight needle could be passed and uniform pressure made on it. The method of making cuts in the heart beating in situ has been described in a previous paper of this series.¹

EXPERIMENTS IN WHICH THE PATH OF CONDUCTION WAS STUDIED
BY MEANS OF COMPARISONS OF ONSET OF NEGATIVITY IN
VARIOUS ELECTRODES

Experiments somewhat similar to the experiments performed in this series have been previously reported by ourselves⁴ and more recently by Lewis.⁷ In our previous work we found a radial spread of the excitation from the node, with a tendency, however, to a more rapid spread of the negativity to the intercaval or venous side of the

TABLE 1.—SEQUENCE OF NEGATIVITY OF THE POINTS SHOWN IN FIGURE 1 *

Experiment	Sequence of Negativity								
1	2	4	3	1	6	7	5	8	9
2	1	4	3	5	7	9 †			
3	1	3	5	4	7	9 †			
4	1	3	5	4	9	7 †			

* In each experiment head of Sa node was shown to be negative to all other points and to Av node.

† Points 2, 6 and 8 were not determined in these experiments.

TABLE 2.—SEQUENCE OF NEGATIVITY OF THE POINTS SHOWN IN FIGURE 2 .

Experiment	Sequence of Negativity											
5	1	2	8	5	4	3	6	9	7	12	11	10
6	2	1	4	3	5	6	9	10	12	11	7	8
7	3	1	2	7	4	8	5	10	11	12	6	9
8	1	2	3	5	6	9	7	4	10	11	8	12
9	2	1	4	3	7	5	6	10	11	9	8	12
10	1	4	2	3	5	7	6	8	9	10	12	11

sino-auricular node than to the auricular side, since points on the former equidistant from the node usually show negativity before points on the right auricle. Lewis is content to state that the excitation spreads radially in all directions from the node. The experiments which we have more recently undertaken were planned with the purpose to study this matter in greater detail and to find, if possible, whether some part of this radial path conducts the excitation more rapidly than all other parts. Ten experiments of this character were

7. Lewis: In Harvey Lectures, 1914-1915, x, 60.

carried out. In four a single circle of points as nearly as possible equidistant from and surrounding the sino-auricular node were compared. Each point was compared with every other point, so that the sequence of negativity could be obtained. To be sure that we were dealing with a normal sino-auricular rhythm, the upper end of the sino-auricular node was also compared with all of these points and with the auriculoventricular node. The disposition of the points compared is shown in Figure 1. The numbers in this figure refer to Table 1, which gives the sequence of negativity of these points in the four experiments. Figure 2 and Table 2 give the corresponding data for the remaining six experiments, in which two circles of points were compared in a similar way to the above.

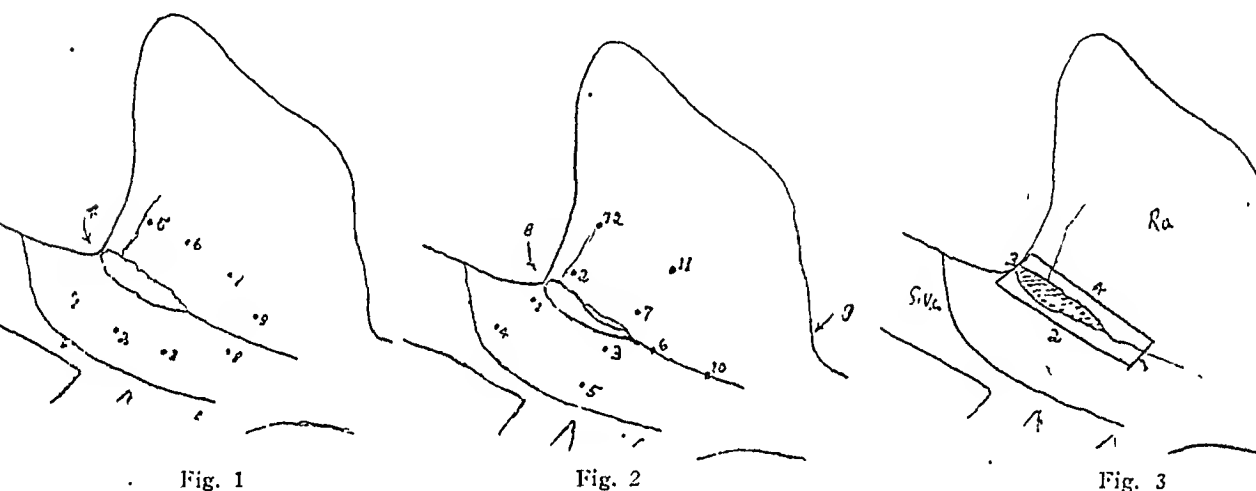


Fig. 1

Fig. 2

Fig. 3

Fig. 1.—Four points along auricle and four points in intercaval region, each pair equidistant from the head of the *Sa* node, compared as to onset of negativity. In addition, comparisons were made between the *Sa* node and the point above the node near the auricular septum (point 4), the same distance from the node as the points on the auricular and the venous side.

Fig. 2.—Point 8 is in a similar position to point 4 of the preceding experiments. Point 9 is on the ventricular portion of the auriculoventricular node.

Fig. 3.—Position and designation of interruptions made around the sino-auricular node.

EXPERIMENTS IN WHICH THERE WAS PARTIAL OR COMPLETE ISOLATION OF THE SINO-AURICULAR NODE

Interruption of the physiologic continuity of the tissues on one or more of the four sides of the sino-auricular node was secured by ligating, clamping or cutting, as previously described. The position of the interruptions is noted in the tables as follows: (1) across the sulcus terminalis, at right angles to the long axis of the sino-auricular node and from 5 to 10 mm. below this structure; (2) along the intercaval or venous border of the sulcus, beginning at the venous end of (1) and ending opposite a point a few millimeters above the head of the node; (3) across the junction of the superior vena cava and

appendage of the right auricle, a few millimeters above the head of the node; (4) along the auricular border of the sulcus, joining the auricular ends of (1) and (3) (Fig. 3). In the summaries in the table no statement is made as to the method of interruption, since the different methods used gave identical results. Interruptions 1 and 3 were frequently but by no means always made by ligation; 2 and 4 always by cutting or clamping, except in a few cases in which multiple ligatures were employed. The series of four interruptions, when complete,

TABLE 3.—RECORD OF CONTRACTIONS OF RIGHT AURICLE AND RIGHT VENTRICLE

Experiment	Procedure	As-Vs, Sec.	Cycle, Sec.	Pacemaker
11	Normal.....	0.100	0.370	Sa
	Cut 4.....	0.100	0.410	Sa
12	Normal.....	0.090	0.350	Sa
	Cut 3.....	0.090	0.350	Sa
	Cut 1.....	0.030	0.470	Av
13	Normal.....	0.120	0.340	Sa
	Cut 4.....	0.12	0.34	Sa
	Cut 3.....	0.12	0.34	Sa
	Cut 2.....	0.03	0.62	Av†
14	Normal.....	0.13	0.40	Sa
	Cut 4.....	0.11	0.43	Sa
	Cut 2.....	0.06	0.45	C.S†
15	Normal.....	0.10	0.36	Sa
	Cut 4.....	0.10	0.36	Sa
	Cut 3.....	0.10	0.40	Sa
	Cut 1.....	0.03	0.40	Sa
	Cut 2.....	0.00	0.50	Av
16	Normal.....	0.18	0.69	Sa
	Cut 4.....	0.18	0.51	Sa
	Cut 1.....	0.18	0.57	Sa
	Cut 3.....	0.18	0.57	Sa
	Cut 2.....	0.03	0.90	Av
17	Normal.....	0.17	0.33	Sa
	Cut 4.....	0.15	0.38	Sa
	Cut 1.....	0.11	0.40	Sa†
	Cut 3.....	0.11	0.40	Sa†
	Cut 2.....	0.05	0.48	Av†
18	Normal.....	0.12	0.42	Sa
	Cut 4.....	0.09	0.40	Sa
	Cut 3.....	0.02*	0.60	Av†
19	Normal.....	0.11	0.35	Sa†
	Cut 4.....	0.12	0.40	Sa†
	Cut 2.....	0.12	0.40	Sa†
	Cut 3.....	0.10	0.47	Sa†
	Cut 1.....	0.06	0.62	C.S†

* To be read Vs-As instead of As-Vs.

† Position of pacemaker confirmed by comparisons of onset of negativity with galvanometer.

entirely surround and isolate the sino-auricular node from the remainder of the heart. Considerable histologic experience has indicated to us the rather marked constancy of the position and extent of the sino-auricular node in the dog's heart, and sufficient margin was given when carrying out the isolation of the node to avoid implication of this structure in the lesions produced. The area isolated included, therefore, in addition to the sino-auricular node a margin

varying from two to three millimeters in width of auricular or inter-caval tissues surrounding the node.

In Table 3 are summarized the results from nine experiments in which the contractions of the right auricle and right ventricle were

TABLE 4.—COMPARISON OF ONSET OF NEGATIVITY MADE BETWEEN FIVE DIFFERENT POINTS

Experiment	Procedure	Sequence of Negativity
20	Normal..... Cut 1.....	Sa-Svc-Av-Cs-Ra Av-Sa-Ra
21	Normal..... Cut 2..... Cut 1.....	Sa-Svc-Av-Cs-Ra Sa-Svc-Ra-A-Cs Sa-Svc-Ra-A-Cs
22	Normal..... Cut 3..... Cut 2.....	Sa-Av-Svc-Cs-Ra Sa-Svc-Cs-Ra-Av Av-Cs-Ra-Svc-Sa
23	Normal..... Cut 1..... Cut 2..... Cut 3.....	Sa-Svc-Av-Ra-Cs Sa-Svc-Ra-Av-Cs Av-Cs-Ra-Svc-Sa Av-Cs-Svc-Sa-Ra
24	Normal..... Cut 1..... Cut 2.....	Sa-Svc-Av-Cs-Ra Sa-Av-Svc-Cs-Ra Av-Cs-Ra-Sa-Svc
25	Normal..... Cut 1..... Cut 2..... Cut 3.....	Sa-Svc-Cs-Ra-Av Av-Ra-Sa-Cs-Svc Av-Ra-Sa-Svc-Cs Av-Ra-Sa-Cs-Svc
26	Normal..... Cut 1..... Cut 2..... Cut 3..... Cut 4*	Sa-Svc-Av-Ra-Cs Sa-Svc-Ra-Cs-Av Sa-Svc-Ra-Cs-Av Sa-Svc-Ra-Cs-Av Sa-Svc-Ra-Cs-Av
27	Normal..... Cut 1..... Cut 2..... Cut 3..... Cut 4.....	Sa-Svc-Av-Cs-Ra Sa-Svc-Av-Cs-Ra Sa-Svc-Av-Ra-Cs Cs-Ra-Av-Svc-Sa Cs-Ra-Av-Svc-Sa
28	Normal..... Cut 1..... Cut 2..... Cut 4..... Cut 3.....	Sa-Svc-Ra-Av-Cs Sa-Svc-Ra-Av-Cs Sa-Svc-Ra-Av-Cs Sa-Svc-Av-Ra-Cs Av-Cs-Ra-Sa-Svc
29	Normal..... Cut 1..... Cut 2..... Cut 4..... Cut 3.....	Sa-Svc-Ra-Av-Cs Sa-Svc-Ra-Av-Cs Sa-Svc-Ra-Av-Cs Sa-Ra-Svc-Cs-Av Cs-Ra-Svc-Av-Sa
30	Normal..... Cut 1..... Cut 2.....	Sa-Av-Cs-Ra-Svc Sa-Ra-Av-Cs-Svc Av-Cs-Sa-Ra-Svc
31	Normal..... Cut 4..... Cut 2..... Cut 1.....	Sa-Svc-Av-Ra-Cs Sa-Svc-Av-Ra-Cs Av-Ra-Sa-Svc-Cs Av-Ra-Cs-Sa-Svc

* Cut 4 was incomplete, about 8 mm. at the upper portion being open.

recorded and the sino-auricular node partially or completely isolated. Galvanometer records were made only in those instances in which the length of the *As-V's* interval did not point to the position of the pace-

maker or when it seemed desirable to confirm this position by another method. The use of the galvanometer in these experiments was confined to comparisons of the onset of negativity between the sino-auricular node, right auricle, coronary series and ventricular portion of the auriculoventricular node. No attempt was made to measure the normal interval of onset of negativity between these regions or the influence on this of the interruption of the connections of the node.

In Table 4 are summarized the results from twelve experiments, in which comparisons of the onset of negativity were made between five different points on the heart, before and after partial or complete isolation of the sino-auricular node. The five points were (1) the upper portion of the sino-auricular node (*Sa*), (2) the mouth of the superior vena cava a few millimeters above its junction with the right auricle (*S.v.c.*), (3) the body of the right auricle (*Ra*), (4) the auricular portion of the auriculoventricular node (coronary sinus, *Cs*) and (5) the ventricular portion of the same node (*Av*). These were compared in couples, the direction of movement of the galvanometer fiber in each case indicating which one of the two points manifested initial negativity. Mechanical systole of the right auricle was also recorded by means of air transmission to a tambour, the lever of which moved in front of the slit of the photographic registration apparatus. A specially devised contact key connected the different electrodes in such a way that any two could be connected through the galvanometer and rapid change made from one couple to another. A complete series of comparisons between all five points could in this way be made over a very short period of time. The interruptions of the tissues around the node are numbered as in the previous table and as indicated in Figure 3.

In Table 5 are summarized the results from thirty-five experiments in which measurements of the intervals of the onset of negativity were made between (1) the sino-auricular node and the ventricular portion of the auriculoventricular node (*Sa-Av*), (2) the sino-auricular node and the body of the right auricle (*Sa-Ra*), and (3) between the ventricular portion of the auriculoventricular node and right auricle (*Av-Ra*). The mechanical systoles of the right auricle and right ventricle were also recorded by air transmission by means of tambours before the slit of the photographic registration apparatus. In many of these experiments records of auricular and ventricular systoles were also made on a Hürthle kymographion, in order to allow measurement of auriculoventricular intervals (*As-Vs*) during the course of the experiments. In certain cases, as noted in the table, the position of the pacemaker was confirmed by direct comparisons of negativity between electrodes placed as in the preceding group of experiments, summarized in Table 4. Determination of the conduction

TABLE 5.—SUMMARY OF RESULTS OF THIRTY-FIVE EXPERIMENTS MEASURING INTERVALS OF ONSET OF NEGATIVITY BETWEEN DIFFERENT PARTS OF HEART

Experiment	Procedure	Sa-Av, Sec.	Av-Sa, Sec.	Sa-Ra, Sec.	Av-Ra, Sec.	Ra-Av, Sec.	As-Vs, Sec.	Cycle, Sec.	Pace- maker
32	Normal.....	0.030	0.025	0.005	0.140	0.550	Sa
	Cut 4.....	0.045	0.030	0.015	0.120	0.580	Sa
	Cut 1.....	0.000	0.040	0.700	C.S.
33	Normal.....	0.025	0.025	0.000	0.090	0.350	Sa
	Cut 2.....	0.050	0.023	0.027	0.080	0.380	Sa
	Cut 3.....	0.010	0.015	0.000	0.470	Av
34	Normal.....	0.040	0.030	0.010	0.097	0.375	Sa
	Cut 3.....	0.055	0.025	0.030	0.095	0.400	Sa
	Cut 2.....	0.055	0.025	0.030	0.090	0.480	Sa
	Cut 4.....	0.020	0.005	0.025	0.000	0.640	Av
35	Normal.....	0.030	0.030	0.000	0.115	0.047	Sa
	Cut 4.....	0.030	0.055	0.025	0.110	0.053	Sa
	Cut 1.....	0.010	0.040	0.050	0.060	0.110	Av
36	Normal.....	0.035	0.035	0.000	0.110	0.330	Sa
	Cut 4.....	0.045	0.105	0.330	Sa
	Cut 3.....	0.025	0.015	0.040	0.090	0.460	Av
37	Normal.....	0.028	0.014	0.042	Av
	Cut 4.....	0.014	Av
38	Normal.....	0.018	0.028	0.020	Sa
	Cut 4.....	0.020	0.005	Av*
39	Normal.....	0.070	0.025	0.005	0.350	Sa
	Cut 4.....	0.013	0.053	0.010	0.350	Sa
	Cut 3.....	0.007	0.007	0.450	?
	Cut 1.....	0.023	0.018**	0.005	0.460	Av
40	Normal.....	0.028	0.020	0.008	0.090	0.140	Sa
	Cut 2.....	0.010	0.013	0.023	0.000	0.650	Av
41	Normal.....	0.024	0.020	0.004	0.100	0.360	Sa
	Cut 2.....	0.005	0.003	0.002	0.075	0.430	C.S.
42	Normal.....	0.022	0.030	0.008	0.070	0.410	Sa
	Cut 4.....	0.016	0.035	0.019	0.070	0.410	Sa
	Cut 1.....	0.070	0.600	Av†
43	Normal.....	0.007	0.012	0.005	0.105	0.420	Sa
	Cut 1.....	0.015	0.015	0.000	0.090	0.420	Sa
	Cut 2.....	0.017	0.011	0.003	0.060	0.420	Sa
44	Normal.....	0.007	0.018	0.011	0.110	0.420	Sa
	Cut 1.....	0.021	0.009**	0.012	0.045	0.545	Av
	Later.....	0.090	0.480	Sa†
	Cut 2.....	0.000	0.000	0.000	0.100	0.560	C.S.†
45	Normal.....	0.032	0.020	0.012	0.120	0.350	Sa
	Cut 1.....	0.043	0.015	0.028	0.140	0.410	Sa
	Cut 2.....	0.046	0.010	0.036	0.110	0.560	Sa
46	Normal.....	0.021	0.016	0.005	0.110	0.350	Sa
	Cut 1.....	0.025	0.012	0.013	0.110	0.370	Sa
	Later.....	0.013	0.000	0.420	Av
	Later.....	0.110	0.410	Sa†
	Cut 2.....	0.032	0.013	0.019	0.110	0.430	Sa
47	Normal.....	0.020	0.013	0.007	0.110	0.420	Sa
	Cut 1.....	0.090	Av
	Later.....	0.036	0.016	0.020	0.165	0.310	Sa
	Cut 2.....	0.037	0.015	0.022	0.160	0.460	Sa†
48	Normal.....	0.028	0.016	0.012	0.095	0.350	Sa
	Cut 1.....	0.024	0.070	0.365	Sa†
	Later.....	0.033	0.016	0.017	0.070	0.350	Sa
	Cut 2.....	0.016	0.020	0.450	Av
	Later.....	0.040	0.020	0.020	0.070	0.410	Sa

TABLE 5.—SUMMARY OF RESULTS OF THIRTY-FIVE EXPERIMENTS MEASURING
INTERVALS OF ONSET OF NEGATIVITY BETWEEN DIFFERENT
PARTS OF HEART—(Continued)

Experi- ment	Procedure	Sa-Av, Sec.	Av-Sa, Sec.	Sa-Ra, Sec.	Av-Ra, Sec.	Ra-Av, Sec.	As-Vs, Sec.	Cycle, Sec.	Pace- maker
49	Normal.....	0.012	0.017	0.005	0.080	0.330	Sa
	Cut 1.....	0.005	0.100	0.310	?
	Later.....	0.023	0.100	0.350	Sa
	Cut 2.....	0.003	0.007	0.015	0.060	0.375	Av
	Later.....	0.033	0.080	0.380	Sa
50	Normal	0.026	0.011	0.015	0.100	0.350	Sa
	Cut 2.....	0.007	0.060	0.420	?
	Cut 1.....	0.023	0.000	0.040	0.480	Av†
51	Normal.....	0.016	0.060	0.380	Av
	Cut 1.....	0.018	0.030	0.380	Av
	Cut 2.....	0.043	0.040	0.370	Av
52	Normal.....	0.030	0.120	0.270	Sa
	Cut 2.....	0.030	0.120	0.270	Sa
	Cut 1.....	0.035	0.120	0.230	Sa
	Cut 3.....	0.003	0.080	0.380	Av†
53	Normal....	0.026	0.020	0.006	0.100	0.430	Sa
	Cut 4.....	0.026	0.026	0.000	0.100	0.460	Sa
	Cut 1.....	0.026	0.026	0.000	0.100	0.520	Sa
	Cut 2.....	0.022	0.000	0.680	Av
54	Normal.....	0.022	0.013	0.009	0.080	0.290	Sa
	Cut 4.....	0.017	0.020	0.003	0.120	0.320	Sa
	Cut 2.....	0.026	0.000	0.026	0.030¶	0.400	Av
55	Normal.....	0.030	0.014	0.016	0.100	0.420	Sa
	Cut 4.....	0.030	0.023	0.002	0.100	0.430	Sa
	Cut 2.....	0.000	0.000	0.080	0.490	C.S.
	Cut 1.....	0.019	0.016**	0.003	0.060	0.490	Av
56	Normal.....	0.024	0.016	0.003	0.120	0.300	Sa
	Cut 2.....	0.024	0.016	0.003	0.120	0.270	Sa
	Cut 3.....	0.024	0.014	0.010	0.110	0.320	Sa
	Cut 1.....	0.31	0.007	0.38	0.000	0.370	Av
57	Normal.....	0.035	0.030	0.005	0.140	0.290	Sa
	Cut 2§.....	0.003	0.090	0.330	C.S.
	Later.....	0.035	0.130	0.330	Sa
	Cut 2§.....	0.035	0.024	0.011	0.125	0.340	Sa
	Cut 1.....	0.031	0.012	0.047	0.040¶	0.370	Av
58	Normal.....	0.027	0.040	0.013	0.220	0.400	Sa
	Cut 3.....	0.037	0.230	0.500	Sa
	Cut 1.....	0.000	0.190	0.550	C.S.†
	Cut 2.....	0.000	0.180	0.540	C.S.
59	Normal.....	0.025	0.100	0.410	Sa
	Cut 3.....	0.040	0.130	0.410	Sa
	Cut 1.....	0.040	0.100	0.380	Sa
	Cut 2.....	0.027	0.045	0.430	Av
	Cut 4.....	0.027	0.045	0.430	Av
60	Normal.....	0.012	0.097	0.370	Sa
	Cut 3.....	0.005	0.020	0.400	Av
	Later.....	0.030	0.080	0.350	Sa
	Cut 1.....	0.036	0.000	0.390	Av
61	Normal.....	0.031	0.200	0.350	Sa
	Cut 3.....	0.069	0.060¶	0.380	Av
	Later.....	0.050	0.165	0.370	Sa
	Cut 1.....	0.050	0.130	0.360	Sa
	Cut 2.....	0.050	0.130	0.400	Sa†
62	Normal.....	0.013	0.083	0.360	Sa
	Cut 3.....	0.005	0.037	0.420	Av
	Later.....	0.016	0.090	0.400	Sa

TABLE 5.—SUMMARY OF RESULTS OF THIRTY-FIVE EXPERIMENTS MEASURING INTERVALS OF ONSET OF NEGATIVITY BETWEEN DIFFERENT PARTS OF HEART—(Continued)

Experi- ment	Procedure	Sa-Av, Sec.	Av-Sa, Sec.	Sa-Ra, Sec.	Av-Ra, Sec.	Ra-Av, Sec.	As-Vs, Sec.	Cycle, Sec.	Pace- maker
63	Normal.....	0.024	0.100	0.320	Sa
	Cut 3.....	0.014	0.060	0.350	Av
	Cut 1.....	0.030	0.090	0.370	Av
	Later.....	0.034	0.090	0.370	Sa
	Later.....	0.020	0.000	0.440	Av
64	Normal.....	0.036	0.160	0.380	Sa
	Cut 3.....	0.042	0.160	0.370	Sa
	Cut 1.....	0.043	0.130	0.430	Sa†
	Cut 2.....	0.019	0.100	0.480	Av
65	Normal.....	0.022	0.152	0.540	Sa
	Cut 1.....	0.050	0.190	0.400	Sa
	Later.....	0.030	0.170	0.500	Sa
	Cut 3.....	0.045	0.180	0.470	Sa
	Cut 2.....	0.014	0.130	0.600	Av
	Later.....	0.030	0.150	0.500	Sa
	Cut 4.....	0.000	0.600	Av
66	Normal.....	0.013	0.104	0.340	Sa
	Lig. 1#.....	0.024	0.100	0.330	Sa
	Lig. 1 relieved....	0.018	0.105	0.380	Sa
	Cut 3.....	0.040	0.110	0.400	Sa
	Later.....	0.032	0.100	0.400	Sa
	Lig. 1.....	0.020	0.025	0.500	Av

* Necropsy showed that Cut 4 involved the upper part of the Sa node.

** To be read Ra-Sa instead of Sa-Ra.

† Position noted shown to be seat of pacemaker by comparison of onset of negativity with other regions.

‡ Comparisons of onset of negativity indicated that pacemaker was in lower portion of Sa node.

§ To be read Vs-As instead of As-Vs.

¶ In this experiment, Cut 2 was made in two parts, the upper half first.

In this experiment Ligature 1 was laid and tied in the usual position of Cut 1. When not otherwise noted, Sa indicates seat of pacemaker in upper part of Sa node.

intervals, as noted above, and of the *As-Vs* interval and length of cycle were made before and after partial or complete isolation of the sino-auricular node. In all cases these determinations represent averages from a number of cycles. The positions of the interruptions surrounding the node are given in Figure 3. In some of these experiments a part of the isolation was carried out by gradual clamping in an attempt to obtain partial sino-auricular or sinoventricular block, and continuous records made with measurements of *Sa-Av* conduction, *As-Vs* interval and length of cycle throughout the whole period of tightening the clamp. The results from this part of the work with other experiments bearing on this problem will be reported in a subsequent paper, and at this time there will be considered only the results on the position of the pacemaker and on the conduction time consequent on complete functional interruption of the clamped tissue.

The rate of conduction of the wave of negativity between the sino-auricular and auriculoventricular nodes and the right auricle was determined in the first five experiments of Table 5 by the procedure first described in the discussion under methods. One galvanometer

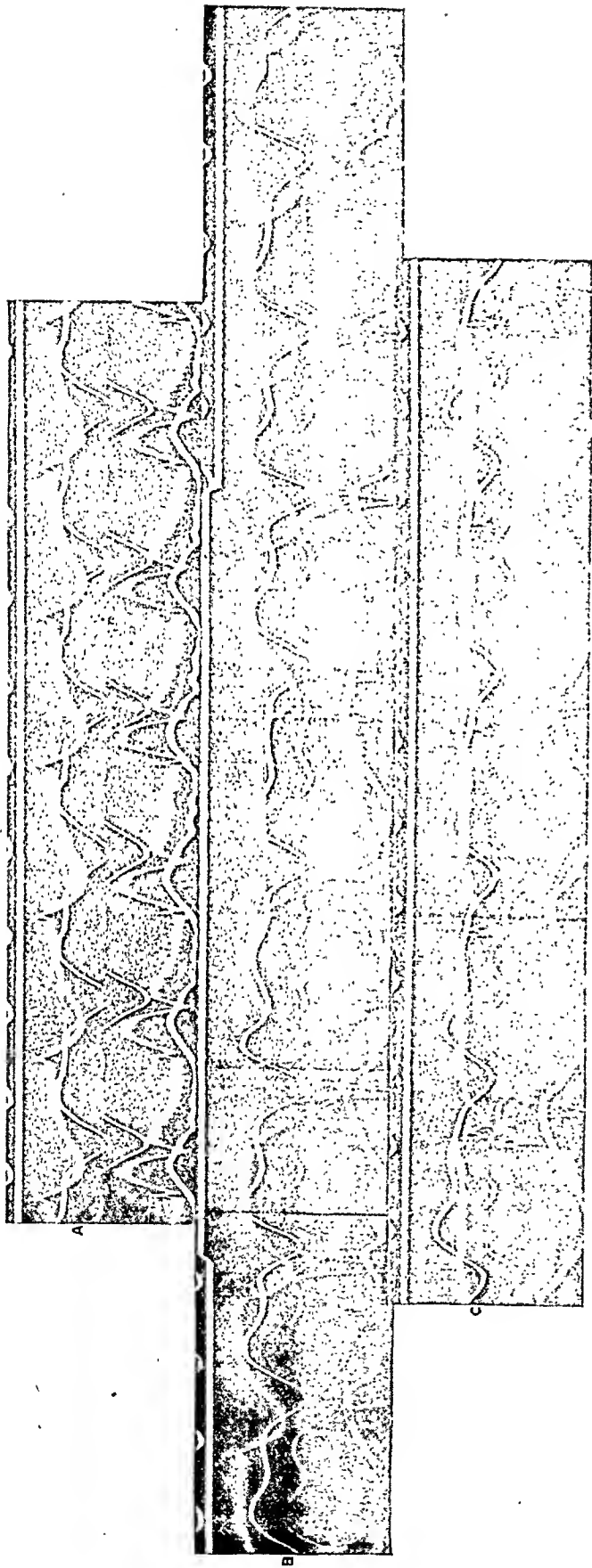


Fig. 4.—The records shown in this figure are to be interpreted as follows, reading from top to bottom: (1) Time record in one-fifth of a second intervals; (2) signal pen; (3) shadow of galvanometer fiber connected to upper and middle portion of sino-auricular node; (4) tambour lever, the downstroke of which indicates the onset of mechanical systole of the right auricle, there being immediately below this a duplicate shadow cast by this lever which should be ignored; (5) galvanometer fiber connected with two points on the auriculoventricular node; (6) tambour lever, indicating by its downstroke mechanical systole of the right ventricle.

The records are all from Experiment 51. *A* is the normal record and shows $Sa-Av=0.013$ of a second, $As-Vs=0.10$ of a second, cycle $=0.36$ of a second. Between this and record *B* a ligature was tied above the sino-auricular node (interruption No. 3). As a result of this $Sa-Av$ has increased, in the first cycle of this record, to 0.036 of a second. During record *B* a ligature was tied below the node (interruption No. 1), as signaled. This caused changes in the rhythm as follows: One auriculoventricular cycle with $Av-Sa=0.035$ of a second, $As-Vs=0.04$ of a second (cycle 2 of record); one normal cycle; one auriculoventricular cycle with $Av-Sa=0.032$ of a second, $As-Vs=0.048$ of a second, cycle $=0.43$ of a second, one cycle with Sa and Av simultaneous, $As-Vs=0.08$ of a second; then a succession of normal cycles with $Sa-Av=0.033$, $As-Vs=0.093$. Tying this ligature thus produced several auriculoventricular cycles, with permanent lengthening of the $Sa-Av$ conduction period in the subsequent sino-auricular cycles.

C shows the condition of permanent auriculoventricular rhythm which developed, without further procedure, five minutes later. $Av-Sa=0.02$ of a second, $As-Vs=0.032$ of a second, cycle $=0.50$ of a second.

was used and the onset in negativity in these different regions compared with the onset of mechanical systole of the right auricle. In the remaining thirty experiments two galvanometers were employed and the second method was used for the determination of the intervals of negativity. One galvanometer was connected with a pair of electrodes placed a few millimeters apart on one region to be compared; the other region had two similar electrodes connected with the second galvanometer. The two electrodes on the sino-auricular node were always connected with the galvanometer in such a way that the upstroke of the galvanometer curve indicated primary negativity in the uppermost of these two electrodes, thus giving additional information in those cases in which the node preceded other regions, whether the pacemaker was in its normal position in the upper part or lower down in the tissues of the node.⁸

SEQUENCE OF NEGATIVITY IN REGIONS NEAR THE SINO-AURICULAR NODE

The first ten experiments, summarized in Tables 1 and 2, show that points on the venous or intercaval side of the sino-auricular node usually manifest initial negativity before equidistant points on the auricular side, and that therefore the excitation should be regarded as spreading as a rule more rapidly in this direction than to the auricle. Experiments of a somewhat similar nature have been reported previously by us⁴ and the same conclusion drawn. The present experiments, however, we believe lead clearly to a further conclusion, namely, that there is no restricted region surrounding the sino-auricular node which invariably receives the excitation before other regions. Considering the distance of any particular region from the node in its relation to the distance of other regions, we see no restricted region which can be regarded as the exclusive path of conduction.

Macroscopic examination of the dog's heart shows two large well-developed masses of musculature passing, respectively, from the upper and lower end of the sulcus terminalis. The former bundle has been described by Curran⁹ in the calf's and sheep's heart as arising from the auriculoventricular node, passing upward along the interauricular septum, and consisting of bundles of musculature which can be traced almost to the mouth of the superior vena cava. That this bundle, however, has no especial significance in the conduction of the excitation from the sino-auricular to the auriculoventricular node is indicated by the fact that the electrodes placed on this structure (electrode 4 in the first four and electrode 8 in the last six experiments) did not

8. Meek and Eyster: *Am. Jour. Physiol.*, 1914, xxxiv, 368.

9. Curran: *Anat. Anz.*, 1909, xxxv, 89.

show negativity before electrodes on other regions equidistant from the node. The same can be said of the somewhat similar bundle, which apparently passes from the lower end of the sulcus terminalis downward toward the coronary sinus (electrode 9 in the first four, electrode 10 in the last six experiments). Furthermore, in two experiments (Experiments 9 and 10) these bundles were ligated during the course of the experiment without influencing the sequence as given in the tables.

SEQUENCE OF NEGATIVITY AND RATE OF CONDUCTION BETWEEN THE
SINO-AURICULAR NODE, RIGHT AURICLE AND AURICULO-
VENTRICULAR NODE

The normal sequence of negativity between the sino-auricular node, right auricle and auriculoventricular node, as given in the normals of Table 4, further emphasize a fact for which we have already submitted evidence,⁴ namely, that conduction from the sino-auricular node to the auriculoventricular node and ventricular conductive system does not normally occur, as has always been held, by way of the body of the right auricle, since the auriculoventricular node frequently receives the excitation before the body of the right auricle (atrium). In the normals of Table 4 the auriculoventricular node preceded in negativity the body of the right auricle in nine of twelve experiments. Measurements of the time intervals of the onset of negativity in the sino-auricular node, the right auricle and auriculoventricular node, as given in the normals of Table 5, while indicating in these experiments a more frequent occurrence of negativity in the right auricle before the auriculoventricular node, point to the same conclusion, because of the frequency of the reverse relation and the occurrence of practically simultaneous negativity in these two regions in other experiments. In twenty-four experiments in this series, the right auricle received the excitation before the auriculoventricular node in fifteen, with an average difference of 0.0091 of a second. The right auricle followed the auriculoventricular node in six experiments with an average of 0.0078 of a second. In three experiments the onset of negativity in the two regions was simultaneous, so far as could be determined from the records. That in any normal case negativity in the auriculoventricular node should precede that in the auricle would seem to preclude conduction to the node by way of the auricle as a normal process. As will be seen later in this paper, the results from the partial isolation of the sino-auricular node indicate most clearly that conduction from the sino-auricular node to the right auricle and the auriculoventricular node occurs by two separate and distinct paths under normal conditions. It may also be concluded that since the right auricle may, and frequently does, receive the excitation before the auriculoventricular,

the right auricle does not normally receive its excitation from the auriculoventricular node.

The normal time of conduction from the sino-auricular node to the auriculoventricular node (*Sa-Av*), as measured by the method of using two galvanometers simultaneously, averaged, in twenty-eight experiments, 0.023 of a second, with variations from 0.007 to 0.048 of a second. Conduction from the sino-auricular node to the beginning of the ventricular conductive system is thus quite rapid, and by far the greater part of the delay in passage to the ventricle must occur within the auriculoventricular node or bundle. The average time of conduction in the intact heart between the sino-auricular node and body of the right auricle or atrium (*Sa-Ra*) was 0.020 of a second in nineteen experiments, as determined by the same method, with variations between 0.012 and 0.04 of a second. With an average *As-Vs* interval of 0.12 of a second, it is evident that the excitation reaches the auriculoventricular node approximately 0.12 of a second before the ventricles enter into contraction. In a series of fourteen experiments previously reported by us⁴ we found a somewhat higher average for the sino-auricular interval, using the first method of measurement described above, namely, 0.027 of second. We regard the method used in the present experiments more accurate and the result to represent more closely the correct value for this interval.

THE EFFECTS OF INTERRUPTION OF THE PATHS OF CONDUCTION

The influences exerted by partial or complete isolation of the sino-auricular node on *Sa-Av* and *Sa-Ra* conduction, and on the seat of the pacemaker, consequent on the procedures carried out in Experiments 11 to 66, are summarized in Table 6; Experiments 37 and 51, which were in auriculoventricular rhythm before any experimental procedures were carried out, are not included in this summary. The classification of the experiments in Table 6 is based on the situation of the single interruptions and the effects produced by isolation of the sino-auricular node on one or more sides.

The following points in reference to the effects produced would seem to be clear from the data presented:

Of the single interruptions, number 2, along the intercaval border of the sulcus, was the most effective in causing permanent auriculoventricular rhythm, which it did in 25 per cent. In 12.5 per cent. transitory auriculoventricular rhythm was established, making a total transitory and permanent removal of the pacemaker from the sino-auricular node of 37.5 per cent. Interruption number 3, across the sulcus above the sino-auricular node, produced transitory auriculoventricular rhythm in 40 per cent., but in no case was this rhythm permanently established, sino-auricular rhythm returning in all cases. Inter-

ruption number 1 caused transitory auriculoventricular rhythm in 10.5 per cent. and in 10.5 per cent. this rhythm was permanently established, a total of 21 per cent. Interruption number 4, along the auricular border of the sulcus, was clearly the least effective in causing a change in the location of the pacemaker, failing to produce in any of seventeen experiments either temporary or permanent removal.¹⁰ Isolation of the node on the auricular side, on the other hand, was very effective in increasing the time of conduction between the sino-auricu-

TABLE 6.—SUMMARY OF RESULTS OF CUTS MADE AROUND THE SA NODE
COMPILED FROM TABLES *

Cuts	Experiment	Sa Rhythm Persisted	Transitory Av Rhythm Developed	Percentage of Total Developing Transitory Av Rhythm	Permanent Av Rhythm Developed	Percentage of Total Developing Permanent Av Rhythm	Percentage of Those Not Developing Av Rhythm That Showed Increase of Sa-Av	Average Increase of Sa-Av, Sec.	Percentage of Those Not Developing Av Rhythm That Showed Increase of Sa-Ra	Average Increase of Sa-Ra
1	19	15	2	10.5	2	10.5	100	0.0115	29	0.0025
2	8	5	1	12.5	2	25	50	0.025	0	
3	10	6	4	40	0	0	100	0.0116	0	
4	17	17	0	0	0	0	14	100	0.0115
1 and 2	16	6	4	25	6	33	100	0.0122	12.5	0.002
1 and 3	9	3	2	22	4	33	100	0.0150		
1 and 4	6	5	0	0	3	50				
2 and 3	4	2	0	0	2	50	50	0.015	0	0
2 and 4	5	1	0	0	4	80				
3 and 4	4	2	0	0	2	50				
1, 2 and 3	11	2	1	9	8	73	100	0.0135		
1, 2 and 4	5	2	0	0	3	60				
1, 3 and 4	4	3	0	0	1	25				
2, 3 and 4	3	1	0	0	2	66				
1, 2, 3 and 4	10	0	10	100				

* Experiment 26, in which Cut 4 was not completed, is not included in the summaries. Experiments 37 and 51, in which Av rhythm was present before any cuts were made, were not included in the summaries. The results in one case of Cut 2 and one case of Cuts 3 and 4 are doubtful and are not included in the summary.

lar node and the right auricle (*Sa-Ra*), which it did in 100 per cent. of all cases (eight) in which this was measured. The average increase was 0.0115 of a second. The other interruptions failed to cause any increase in *Sa-Ra* conduction time, except in number 1, which showed an apparent increase of 0.0025 of a second in 29 per cent. of the cases,

10. Experiment 37, in which such a change did occur, is excluded from the totals, since examination showed that the interruption involved a considerable portion of the sino-auricular node.

an amount probably too small to possess any significance and close to the limit of accurate measurement. Conduction from the sino-auricular to the auriculoventricular node (*Sa-Av*), in those cases in which the seat of impulse formation remained in the sino-auricular node, was much less frequently increased by isolation on the auricular side of the node than on the other sides. Interruption number 4 produced this effect only once in seven experiments (1 per cent.). Interruption of the intercaval connections caused an increase in this time in three of six experiments, interruption of the connections below the node in all of seventeen experiments, and interruption above the node in all of ten experiments. The general average of increase in *Sa-Av* conduction from interruptions 1, 2 and 3 was 0.0121 of a second. It therefore seems clear that interruptions above, along the intercaval border and below the sino-auricular node interfere more or less in almost all experiments with conduction from the sino-auricular to the auriculoventricular node. This interference may be sufficient to block the impulse completely and lead to auriculoventricular rhythm, or it may merely prolong the period of conduction. These do not interfere, to any important degree, with conduction from the sino-auricular node to the right auricle. This latter effect is the pronounced influence exerted, however, by interruption of the connections along the auricular side of the node. Such interruption, however, rarely influences conduction from the sino-auricular to the auriculoventricular node.

Isolation of the node on two sides was more effective in producing a change in the seat of the pacemaker than isolation on any one side. Interruptions 2 and 4 were apparently the most effective, permanent auriculoventricular rhythm being established in 80 per cent. of all cases. The other combinations were about equal in reference to number of transitory and permanent changes in the pacemaker. Interruptions 1 and 3 formed a total of 63 per cent. of permanent (38 per cent.) and transitory (25 per cent.) auriculoventricular rhythms and consistently increased *Sa-Av* conduction in those cases in which this rhythm was not permanently established. On interruption of the connections on three sides of the node, interruptions 1, 2 and 3 had the greatest effect, producing permanent (73 per cent.) or transitory (9 per cent.) auriculoventricular rhythms in 82 per cent. of all cases, and in all the remainder increasing *Sa-Av* conduction time. Interruptions 1, 2 and 4, and 2, 3 and 4 produced less effect in those experiments than when 2 and 4 were made alone, probably indicating that the incidence of 80 per cent. of permanent auriculoventricular rhythm from 2 and 4 alone is high and would be reduced by a longer series of experiments. Interruption of the connections of the sino-auricular node on all four sides produced permanent auriculoventricular rhythm in all of ten experiments.

POSSIBILITY OF INFLUENCES EXERTED THROUGH ANEMIA OR
THROUGH THE VAGUS MECHANISM

It was thought possible that one or both of two influences, associated with the isolation of the node, other than that of interruption of paths of conduction, might play a part in the results obtained, namely, (1) decrease in blood supply to the sino-auricular node, (2) mechanical or other stimulation of cardio-inhibitory fibers, in the neighborhood of the lesions. In reference to the first possibility, Keith and Flack,¹¹ Koch¹² and others have called attention to the abundant blood supply to the node. A prominent branch of the right coronary artery passes through the long axis of the node to unite above with a branch from above, forming what has been termed the *circulus arteriosus sino-auricularis*. Numerous branches are given off from this artery in its passage through the node. In several experiments we have tied the main vessel supplying the node without, however, the node losing its function as pacemaker and without producing any measurable change in conduction from the node to the auricle or to the auriculoventricular node. In this connection it is important to note that interruptions 1 and 3 were those which abolished the direct supply of blood to the node through the coronary arteries, after which the node was supplied with blood only through anastomoses on the venous and auricular side and by direct contact of the blood within the heart cavity. The fact that interruption 2, along the venous border of the node, was the most effective in permanently abolishing sino-auricular rhythm, while it probably interfered least of any with the blood supply, would further indicate that decrease in the blood flow to the nodes was not a very important factor in causing a loss of the pacemaking function by this structure. The main factor in the loss of this function and its assumption by some other region, as a result of partial isolation of the node, would therefore seem to be due more to interruption of paths of conduction from the node to the remainder of the heart and a consequent decrease or loss of its influence on the heart as the seat of dominant automaticity, rather than to a reduction in its automaticity below the point of dominance by anemia. In several experiments we have obtained clear proof that the sino-auricular node may continue to function and discharge impulses at a higher rate than the auriculoventricular node at a time when the latter is acting as pacemaker for the heart, the impulses from the former being prevented from reaching other parts of the heart because of interruption of the paths of conduction. This condition is complete sino-auricular and sinoventricular heart block. The discussion of these experiments in detail will be

11. Keith and Flack: *Jour. Anat. and Physiol.*, 1907, xli, 172.

12. Koch: *Med. Klin.*, 1912, viii, 108; *ibid.*, 1913, ix, 1.

found in a subsequent paper. We have seen the sino-auricular node in the heart in situ, but completely separated from all physiologic connection with the remainder of the heart, continue in activity at approximately its normal rate for considerable periods of time. Under these circumstances the interruption of its circulation through the coronary arteries is complete and it receives its blood supply only by contact with the blood within the interior of the heart. Perhaps the same degree of anemia, if acting for a prolonged period of time, would ultimately depress the tissues to the point at which activity would be much reduced or would disappear. It will be noted in Tables 3 and 5 that not infrequently interruptions which did not cause a removal of the seat of the pacemaker from the sino-auricular node produced a slight slowing of the rate of discharge, as is evident from the somewhat longer cycle. This increase in length of cycle indicates a slight reduction in the automaticity of this region, caused perhaps by partial interruption of its blood supply. It would seem, therefore, that while reduction in the blood supply as a result of interrupting the connections of the node may have been in our experiments in some or all cases a contributing factor in the loss by this region of its function as pacemaker for the heart, it was not the most important factor in this change. The latter, we feel, must be referred to interruption of the paths of conduction to other regions and as a consequence the blocking of the impulses from the sino-auricular node until the automaticity of some other region assumed dominance.

The possibility that the effects produced by isolation of the node by clamping or cutting might be ascribed to an effect produced through the vagus, we have eliminated by the administration of atropin in amounts sufficient to completely paralyze the vagus mechanism throughout the course of the experiment. This procedure has been carried out in a sufficient number of experiments to establish the fact that it is without effects on the results produced.

SINO-AURICULAR AND SINOVENTRICULAR CONDUCTION PATHS

We believe that our experiments point clearly to the conclusion that there is no single, well-defined and localized path which serves to the exclusion of others for the conduction of the excitation from the sino-auricular to the auriculoventricular node. At least it may be said that if there is such a path, other paths are present which are capable of conducting the excitation with almost equal facility. As the possible connections between these two nodes are gradually interrupted, there are two results which come out clearly in most of the experiments, first, a lengthening of the time of conduction, and second, its abolition. The latter is associated with the removal of the impulse initiation to the auriculoventricular node. It seems to us that these

results may be interpreted in one of two ways, either that a diffuse path of conduction between the two nodes normally exists, including perhaps all of the tissue surrounding the sino-auricular node except along its auricular border, and that interruption of any part of this path delays or finally abolishes conduction merely by restricting the path to an amount of tissue too small to conduct, or it may be supposed that a part of this represents a more or less well-localized path in which conduction occurs under normal conditions with greatest facility and most rapidly. Removal of this would result in conduction, at a slower rate, over other paths. It may be said, finally, that if there is such a localized path of least resistance its exact position must vary in different hearts. Certain of our experiments indicated the possibility of such a path existing across the intercaval tissues, since it is this region which usually receives the excitation somewhat earlier than the tissues above or below the sulcus terminalis, and further, that interruption 2, which severed this connection, was on the whole the most effective one in abolishing sino-auricular rhythm. It should be noted, however, that the separation of tissue involved in this cut was greater than in either interruption 1 or 3, and that, furthermore, since sino-auricular rhythm may be abolished or *Sa-Av* conduction time definitely increased from either interruption 1 or 3, the assumption of this intercaval path as the path of least resistance does not hold in many cases. Interruptions 1 and 3 either caused a change in the seat of the pacemaker or a lengthening of the *Sa-Av* conduction time in all cases in which this was determined in our experiments, and there would seem, therefore, to be as much and perhaps more reason to ascribe to one or the other of these connections the path of least resistance.

The results from interruption of the connections on different sides of the sino-auricular node, however, serve to distinguish clearly two definite and distinct paths, by one of which the excitation is conducted from this node to the right auricle, by the other from the node to the auriculoventricular node and ventricular conductive system. Interruption 4, which severed the direct continuity of the sino-auricular node and the tissues of the right auricle except for possible small connections at the upper and lower extremities of the node, increased the conduction time between the sino-auricular node and the right auricle in all of seventeen experiments. In none of these did it cause a removal of the seat of impulse initiation from the sino-auricular node, and in only 14 per cent. was there any increase in conduction between this node and the auriculoventricular node. On the other hand, interruptions, 1, 2 and 3, which severed possible paths of conduction below, on the intercaval side and above the node, in the great majority of instances caused either the development of auriculoventricular rhythm or lengthened *Sa-Av* conduction time. The influence of this interruption on *Sa-Ra* conduction time, in those cases in which it apparently

occurred, was too small to be of any significance. These results confirm by another method a conclusion at which we have previously arrived,⁴ namely, that normally conduction from the sino-auricular node to the right auricle, on the one hand, and to the auriculoventricular node, on the other hand, occurs by separate paths. The excitation, arising normally in the sino-auricular node, spreads directly to the right auricle, probably in a diffuse manner, from the auricular side of the node. It also spreads to the auriculoventricular node by paths, probably also diffuse in nature, connecting with the upper, intercaval border and the lower end of the sino-auricular node. We cannot, therefore, in accuracy speak of auriculoventricular conduction in the normal dog's heart. There is an auriculoventricular interval, which is determined by the conduction in three paths, namely, (1) between the sino-auricular node and the right auricle, (2) between this node and the auriculoventricular node, and (3) between the auriculoventricular node and the ventricles.

While it is clear in the normal dog's heart conduction from the sino-auricular node to the auriculoventricular node does not occur by way of the auricle, conduction in this manner may occur in certain cases when the normal paths of *Sa-Av* conduction are interrupted. Sino-auricular rhythm may continue (27 per cent. in eleven experiments), in which the sino-auricular node is cut off from all connections except the auricle. Conduction to the auriculoventricular node in those cases can occur only by way of the right auricle. Reference to the tables will show that these instances showed abnormally long *Sa-Av* conduction periods.¹³ It is possible that connections between the right auricle and auriculoventricular node exist in all cases, but conduction over this path is more difficult than the normal sinoventricular path. In a majority of cases possible conduction to the auriculoventricular node by way of the right auricle would seem to be so difficult that auriculoventricular rhythm develops when the normal functional path between the sino-auricular and auriculoventricular nodes is interrupted.

RELATIVE AUTOMATICITY OF THE SINO-AURICULAR NODE, THE
AURICULAR PORTION OF THE AURICULOVENTRICULAR NODE
(CORONARY SINUS), AND THE VENTRICULAR PORTION
OF THE AURICULOVENTRICULAR NODE

Those experiments in which auriculoventricular rhythm developed as a result of partial or complete isolation of the sino-auricular node make it possible to determine the automaticity or rate of impulse

13. Note also, as shown in Table 4, that under these circumstances the auriculoventricular node always followed the right auricle in negativity, usually a reversal of the normal relation in these experiments.

formation of this region, as compared with the normal pacemaker, the sino-auricular node. We⁸ have previously shown that the upper and lower end of the sino-auricular node differ in automaticity, and Zahn¹⁴ has shown similar differences within the auriculoventricular node. When auriculoventricular rhythm develops as a result of loss of the influence of the sino-auricular node, it is reasonable to assume that the seat of impulse formation is in the most automatic portion of the auriculoventricular node. It is this part, therefore, and its relation to the automaticity of the sino-auricular node which possesses the greatest interest. In a few of our experiments, after loss of the pace-making function by the sino-auricular node, the seat of impulse initiation was found to be in the region surrounding the mouth of the coronary sinus, a part of the system of nodal tissues, which is connected with and forms a part of the auriculoventricular node. Aschoff,⁶ who first demonstrated this connection, designated it as the auricular portion of the auriculoventricular node, while the main mass of this node, lying within the interauricular septum, was termed the ventricular portion. It is this latter part from which the auriculoventricular bundle and ventricular conductive system arises.

Coronary sinus rhythm is usually, but not always, associated with shortening of the *As-Vs* interval and increase in length of the cycle over that present in sino-auricular rhythm. The *As-Vs* interval has not been less than 0.04 of a second in any instance in our experience. Probably the only absolutely definite criterion for coronary sinus rhythm is the occurrence of initial negativity in the coronary sinus region. In our experience, however, the occurrence of practically simultaneous negativity in the sino-auricular node and the ventricular portion of the auriculoventricular node has been always associated with the seat of impulse initiation in the coronary sinus region.

The condition in which the seat of impulse initiation is in the ventricular portion of the auriculoventricular node, auriculoventricular rhythm, is likewise probably only definitely determined by the localization of initial negativity in this region.¹⁵ Shortening of the *As-Vs* interval to less than 0.04 of a second or the presence of a *Vs-As* interval in a continuous rhythm in which the auriculoventricular node was intact, has always been associated with the pacemaker in this node

14. Zahn: Arch. f. d. ges. Physiol., 1913, cli, 247.

15. The use of local heating as a method for determining the location of impulse initiation, which has been somewhat extensively employed in recent work, particularly by Ganter and Zahn and by Zahn, is open to the objection that the response of a certain region may be the result of increase of its automaticity by the heat until it becomes the pacemaker, and does not necessarily mean that it was the seat of impulse initiation before the heat was applied. Local cooling may likewise drive the pacemaker to some other region. The electrical method seems certainly to offer the least objection.

in our experience. In other cases of auriculoventricular rhythm the shortening of the *As-Vs* interval has been slight, although uniformly present. Reference to Table 5 will show one case in which the *As-Vs* interval was 0.13 of a second, two cases in which it was 0.09 of a second, one in which it was 0.08 of a second and one in which it was 0.07 of a second. Decision as to the presence or absence of auriculoventricular rhythm, on the basis of the *As-Vs* interval, would seem to be valueless unless this interval shortens to 0.03 of a second or below, or becomes reversed (*Vs-As*). A moderate shortening of the *As-Vs* interval may be associated with (1) removal of the pacemaker to the lower end of the sino-auricular node,⁸ (2) development of coronary sinus rhythm, (3) development of auriculoventricular rhythm, (4) probably in certain cases with no change in the seat of impulse initiation, but as a result of changes in conduction. To decide definitely which one of these is the associated condition, one must determine the seat of impulse initiation by the electrical method or by local heating or cooling.

In thirty-four experiments¹⁶ the heart in auriculoventricular rhythm, in which the seat of impulse initiation was in the ventricular portion of the auriculoventricular node, showed an increase in length of the cycle in percentage of the cycle of normal sino-auricular rhythm of an average of 33 per cent. The most automatic portion of the auriculoventricular node in the dog's heart may therefore be regarded as having an average automaticity equal to 67 per cent. of the automaticity of the sino-auricular node. In other words, if the average dog's sino-auricular node is capable of initiating impulses at the rate of 100 per minute, the auriculoventricular node has the power to initiate impulses, when freed from the domination of the sino-auricular node, of 67 per minute. Great variations are encountered, however, in different animals. In the thirty-four experiments the decrease in rate associated with the development of auriculoventricular rhythm varies from 5 per cent. to 82 per cent. An average of eighteen experiments, in which during the auriculoventricular rhythm there was a *Vs-As* interval or an *As-Vs* interval of less than 0.04 of a second, showed an average decrease over the original sino-auricular rate of 37 per cent. An average of fifteen, in which the *As-Vs* interval was 0.04 of a second or longer, showed a decrease of 29 per cent. The decrease in rate would seem, therefore, to be somewhat greater when there was a marked change in the *As-Vs* interval. There are, however, wide variations in the individual cases from the averages.

16. One experiment was omitted from the averages (Experiment 58) because it differed so widely from the remainder and showed normally an excessively long *As-Vs* interval.

Coronary sinus rhythm showed an average reduction of 29 per cent. in rate of impulse formation as compared with the normal sino-auricular rhythm in seven experiments, indicating an average automaticity of this region equal to 71 per cent. of the normal sino-auricular rhythm. The extreme variations in the different experiments were 13 per cent. and 77 per cent. In one experiment (Experiment 19), the great difference between the automaticity of the sino-auricular node and the region of next lower automaticity (77 per cent.) was further indicated by the necessity of completely isolating the sino-auricular node on all four sides before the seat of impulse initiation changed (to the coronary sinus region). If this experiment is left out of the average, the reduction of the automaticity in coronary sinus rhythm amounted to only 20.5 per cent. of the previous automaticity, with variations between 13 per cent. and 33 per cent.

It would seem clear from the data presented above that the coronary sinus region or the auricular portion of the auriculoventricular node may show a somewhat higher automaticity than the ventricular portion of the same node in certain animals under certain conditions. Further, the general average of coronary sinus automaticity, when developed, is somewhat higher than that of the ventricular portion of the auriculoventricular node. The usual result of ablation of the sino-auricular node is, however, the assumption of impulse by the latter region. This, as we have seen, occurred in thirty-four of forty-one experiments in this series (83 per cent.). It is difficult to understand why coronary sinus rhythm does not develop more frequently on the basis of the average comparative automaticity of this region. On the basis of the well-known fact that automaticity may be increased by stimulation, it is possible that the somewhat exposed position of the coronary sinus region as compared with that of the ventricular portion of the auriculoventricular node leads under certain experimental conditions to the development of an abnormal degree of automaticity in the former region, and in these exceed the normal automaticity of the latter. Brandenburg and Hoffmann¹⁷ were the first to note the tendency of a rhythm other than the usual auriculoventricular rhythm to develop when rather rough mechanical procedures, such as clamping, were used to destroy the sino-auricular node. The authors thought the pacemaker, under these circumstances, was in a diffuse area in the right auricle, but Zahn¹⁴ later showed that it was a coronary sinus rhythm with the pacemaker in the auricular portion of the auriculoventricular node. We¹ have reported similar experiences in a preceding paper of this series.

17. Brandenburg and Hoffmann: *Med. Klin.*, 1912, viii, 16.

CONCLUSIONS

1. In the dog's heart the cardiac impulse, arising within the upper part of the sino-auricular node, is conducted to the right auricle and to the auriculoventricular node by two separate paths. The former is a diffuse path represented by the contact of the right auricle with the node. The latter path is either also diffuse in nature, involving connections above, below and on the intercaval borders of the node, or there are numerous possible paths offering varying degrees of resistance to the passage of the impulse.

2. The normal period between the occurrence of negativity in the sino-auricular node and in the right atrium averages 0.02 of a second in the dog's heart in situ. The average period of conduction between the sino-auricular node and the ventricular portion of the auriculoventricular node is 0.023 of a second. These conduction periods may be increased from two to two and a half times by partial interruption of the paths concerned.

3. The effects of partial elimination of the connections between the sino-auricular node and the auriculoventricular node are the occurrence of an increased period of conduction between the sino-auricular and auriculoventricular nodes; the cessation of conduction over the normal path with conduction by way of the right atrium; and the cessation of the conduction over the normal path and the occurrence of auriculoventricular rhythm or coronary sinus rhythm.

4. The effects of complete interruption of functional connections between the sino-auricular node and other parts of the heart, or reduction of these connections below a certain value, results in removal of the seat of impulse initiation. In a total of forty-one experiments, in thirty-four the pacemaker was located in the ventricular portion of the auriculoventricular node, in seven in the auricular portion of this node (coronary sinus region).

5. In the dog's heart under the conditions of these experiments, the ventricular portion of the auriculoventricular node showed the capacity to develop automaticity equal to an average of 67 per cent. of the normal automaticity of the sino-auricular node. The auricular portion of the auriculoventricular node showed a similar average of 71 per cent. of the degree of sino-auricular automaticity, although this region developed automaticity much less frequently than the ventricular portion of the auriculoventricular node.

A METABOLISM STUDY OF GOITER

WITH THE EFFECT OF THYROID AND THYMUS TREATMENT *

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Many studies on the feeding of thyroid and thymus have been made on various animals and man, in normal and in pathologic conditions. The results obtained have in many cases been contradictory, although the majority of observers agree that loss of weight and increase of protein metabolism occur in the feeding of thyroid gland to normal animals and man, and that the effect on metabolic processes is more marked in hypothyroidism and in hyperthyroidism. The results with thymus feeding have so far not been encouraging.

Scholz¹ conducted rather complete experiments with a woman suffering with exophthalmic goiter and with a normal person on the same treatment for comparison. Each subject was studied for two periods of from three to five days each, one without thyroid treatment and the other on dried thyroid gland substance. His goiter patient, without treatment, stored 7.437 gm. and on thyroid substance 7.09 gm. nitrogen per day. For the normal control with thyroid treatment the daily nitrogen retention fell from 3.76 to 2.64 gm. That the data from this patient were typical has not yet been demonstrated, but similar though less marked results have been obtained on animals by Roos and others. Roos,² using a dog weighing 11.943 kg., to which 25 gm. of fresh thyroid were given for six days, records an increase of urinary nitrogen from 4.32 to 6.27 gm. and a diminution of 1.82 kg. in weight. A further dose of 30 gm. fresh gland caused a decrease to 4.09 gm. urinary nitrogen and a lowering of body weight to 9.956 kg. Roos showed that the administration of thyroid substance to a thyroidectomized dog increased the nitrogen and sodium chlorid elimination to a greater degree than when thyroid was given to the normal dog. He concluded that the thyroid has a decided influence on phosphorus and nitrogen metabolism, the nature of which was as yet obscure.

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* From the Departments of Physiological Chemistry and the Practice of Medicine of Jefferson Medical College of Philadelphia.

* Reported before American Society of Biological Chemists, Boston, December, 1915.

1. Scholz: *Zentralbl. f. inn. Med.*, 1895, xvi, 1041, 1069.

2. Roos: *Ztschr. f. physiol. Chem.*, 1895, xxi, 19.

A patient of Matthes,³ who was given her own dried excised gland, showed increased nitrogen excretion. David's⁴ patient, on thyro-iodin, excreted 90 per cent. more nitrogen. Scholz¹ and Hirschloff⁵ in similar cases of exophthalmic goiter report retention of nitrogen and gain in weight.

Magnus-Levy⁶ established the fact that in exophthalmic goiter the energy requirements increased from 50 to 70 per cent. above the normal and he showed in cretinism and myxedema⁷ that the heat production was as much as 45 to 50 per cent. below normal; that thus the respiratory quotient in the above diseases is low, but in exophthalmic goiter⁸ high. Dubois⁹ gave an instance of a cretin whose total energy requirement was increased by thyroid treatment from 18 to 25 per cent. above the normal. Magnus-Levy⁸ and Anderson and Bergmann¹⁰ also found thyroid gland produced marked effects of this nature on normal men.

Schöndorff,¹¹ using a dog as subject, obtained a loss of nitrogen of 0.66 gm. in a twelve days' foreperiod, and of 0.12 and 1.13 gm., with a loss in weight in two periods of forty-six days under the influence of varying doses of dry and fresh gland respectively. Schöndorff considered that the protein metabolism at first was not affected; that the body fat was used up, and that increased nitrogen output was due to an increased excretion of nitrogenous extractives, already formed and retained in the body. He considered that protein metabolism was later upset.

Georgiewsky, Richter, Gluzinski and Lemberger, Voit, and Ostwald¹² also obtained with thyroid feeding loss of weight in dogs. Schäfer¹³ found that the addition of small amounts of thyroid tissue to the diets of white rats greatly increased the food consumption, especially in quite young individuals, and accelerated growth and nitrogen retention. Farrant¹⁴ in a recent paper reports increased appetite and loss of weight in cats and in rabbits after thyroid feeding. Hewitt¹⁵

3. Matthes: *Verhandl. d. Cong. f. inn. Med.*, 1897, 232.

4. David: *Ztschr. f. Heilk.*, 1897, xvii, 439.

5. Hirschloff: *Ztschr. f. klin. Med.*, 1899, xxxvi, 200.

6. Magnus-Levy: *Berl. klin. Wchnschr.*, 1895, xxx, 650.

7. Magnus-Levy: *Ztschr. f. klin. Med.*, 1904, lii, 201.

8. Magnus-Levy: *Ztschr. f. klin. Med.*, 1897, xxxiii, 269; *Ibid.*, 1906, lx, 177.

9. Dubois: *Jour. Am. Med. Assn.*, 1914, lxiii, 827; *THE ARCHIVES INT. MED.*, 1916.

10. Anderson and Bergmann: *Skand. Arch. f. Physiol.*, 1898, viii, 326.

11. Schöndorff: *Arch. f. d. ges. Physiol.*, 1897, lxvii, 385.

12. Georgiewsky: *Ztschr. f. klin. Med.*, 1897, xxxiii, 153. Richter: *Centralbl. f. inn. Med.*, 1896, xxii, 65. Gluzinski and Lemberger: *Centralbl. f. inn. Med.*, 1897, xviii, 89. Voit: *Ztschr. f. Biol.*, 1897, xxxv, 116. Ostwald: *Ztschr. f. physiol. Chem.*, 1899, xxiv, 39.

13. Schäfer: *Quart. Jour. Exper. Physiol.*, 1912, v, 203.

14. Farrant: *Brit. Med. Jour.*, 1913, ii, 1363.

15. Hewitt: *Quart. Jour. Physiol.*, 1914, viii, 113.

found that 0.5 gm. doses of thyroid administered to rats gave a greater nitrogen retention than larger doses.

Scholz, Richter, and Gluzinski and Lemberger obtained a diminished positive nitrogen balance after thyroid administration. Cramer and Krause¹⁶ found that the administration of thyroid gland affected carbohydrate metabolism. A further proof of this action on carbohydrate and also on fat metabolism is afforded by the observations of Thiele and Nehring and Stüve¹⁷ that in the case of a normal man to whom thyroid was given the gaseous exchange was greatly increased.

On the other hand, the administration of the gland has in some cases in man (Magnus-Levy) and in dogs (Underhill and Saiki and Rahel Hirsch¹⁸) been found to cause no alteration in metabolism. Similar results in the case of a normal man were obtained by Magnus-Levy¹⁹ who found no distinct increase of oxygen intake or carbon dioxid output while administration of thyroid to a patient with myxedema caused an increase in oxygen intake of 80 per cent. Underhill and Saiki found that thyroid fed to normal dogs effected a slight increase in urinary nitrogen. Small doses appear to have as pronounced an effect as larger ones. In the case of two patients, Scholz and Hirschloff observed with marked daily gain in weight not the slightest disturbance in nitrogen balance.

Unlike thyroid, thymus fed or injected into animals has appeared to have no effect on nitrogen metabolism. Extirpation experiments, however, indicate some connection between the thymus and growth of the skeleton, that is, calcium metabolism.

Carbone²⁰ appears to have found on thymectomized dogs and rabbits a slight increase in nitrogen in both urine and feces. Mikulicz, Reinbach, and Cunningham²¹ report an effect on goiter by thymus, similar to that of thyroid. Magnus-Levy reports two cases in which feeding thymus in exophthalmic goiter for longer or shorter periods was found to have no effect on oxygen consumption. Basch²² on thymectomized animals in comparison with controls of the same litter

16. Cramer and Krause: *Proc. Roy. Med. and Chir. Soc., London*, 1913, lxxxvi, 550.

17. Thiele and Nehring: *Ztschr. f. klin. Med.*, 1896, xxx, 41. Stüve: *Festschr. der Stadtischen Krankenhauses im Frankfort-am-Main*, September, 1896.

18. Underhill and Saiki: *Jour. Biol. Chem.*, 1908, v, 225. Hirsch: *Oppenheimer's Handbuch der Biochemie*, Jena, 1910, iii, 271.

19. In Von Noorden: *Metabolism and Practical Medicine*, American edition, Chicago, 1907, iii.

20. Carbone: *Gior. d. r. Accad. di med. di Torino.*, 1897, ix, 7.

21. Mikulicz: *Berl. klin. Wchnschr.*, 1895, xxxii, 342. Reinbach: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1898, iii, 309. Cunningham: *Jour. Exper. Med.*, 1896, iii, 227.

22. Basch: *Ztschr. f. exper. Path. u. Therap.*, 1905, ii, 95.

obtained twice as great a calcium excretion. Roos²³ on a dog found that child's thyroid, with an iodine content of 0.025 per cent., given in doses of 5 gm. of dried substance caused no effect, while gland containing 0.18 per cent. in like amount produced increased nitrogen excretion.

Age affects the results obtained in an artificially produced condition of hyperthyroidism. Vermehren²⁴ states that patients of over 50 years of age show a greater increase of protein metabolism than children, while Georgiewsky¹² found that in dogs the reverse was the case, young animals reacting more readily than adults.

Perhan²⁵ studying the influence of thyroid principle on calcium metabolism in rabbits, showed that the ingestion of thyroid caused a loss of calcium from the tissues, which ran parallel to the amount of thyroid ingested. Falta, Bolaffio, and Tedesco²⁶ after parathyroidectomy found that thyro-iodine brought about increased excretion of calcium in the feces.

Schäfer,¹³ feeding thyroid to white rats, observed an increased calcium and magnesium excretion. His average variations are considerable and so render the results somewhat doubtful. In a case of myasthenia gravis, which may be an intoxication, Diller and Rosenbloom²⁷ have shown that a marked loss of calcium from the tissues obtains by way of the urine. In a period of eight days they found that 5.7 gm. of calcium oxide, out of a total excretion of 6.3 gm., was eliminated by this channel. Pemberton²⁸ also obtained in myasthenia gravis a similar loss of calcium from the tissues. Scholz found an increased excretion of alkaline earth elements in three cretins. He made complete mineral balances and concluded as a result of his extensive experiments that the metabolism in cretins is sluggish. Basch²⁹ found that injections of soluble calcium salts brought back the irritability to normal in the case of thymectomized dogs with changed psychical nature. Attempts³⁰ have been made to explain the influence on calcification by ascribing to the thymus a detoxicating action in building up acids circulating in the blood into nucleoprotein of the thymus. This suggestion has not been supported by sufficient experi-

23. Roos: *Ztschr. f. physiol. Chem.*, 1899, xxviii, 40.

24. Vermehren: *Deutsch. med. Wchnschr.*, 1893, xix, 255, 1037.

25. Perhan: *Compt. rend Soc. de biol.*, 1913, lxxii, 620.

26. Falta, Bertelli, Bolaffio, Tedesco, and Rudinger: *Verhandl. d. Cong. f. inn. Med.*, 1909, xxvi, 138.

27. Diller and Rosenbloom: *Am. Jour. Med. Sc.*, 1914, cxlviii, 65.

28. Pemberton: *Am. Jour. Med. Sc.*, 1910, cxxxix, 816.

29. Basch: *Jahrb. f. Kinderh.*, 1906, lxiv, 285; *Wien. klin. Wchnschr.*, 1903, xxxi, 893; *Deutsch. med. Wchnschr.*, 1913, xxxix, 1456.

30. Dmitricwski: *Jahresb. ü. d. Fortschr. d. Thierchem.*, 1900, xxx, 778.

mental evidence. Towles³¹ found no disturbance in the metabolism of calcium in exophthalmic goiter.

The older investigators on phosphorus metabolism during thyroid feeding determined phosphorus in the urine alone; they failed to consider fecal elimination. In thyroid feeding to normal men or animals or after thyroidectomy in both, the phosphorus may be excreted in increased amount either in the urine or feces. The amount depends on the size of the dose given. Phosphorus excretion may follow the nitrogen elimination or there may be a retention of phosphorus. Scholz found in a metabolism study of exophthalmic goiter (in a woman) that without thyroid treatment there was a loss of 2.09 gm. per day. In the case of a normal man ingesting thyroid the phosphorus pentoxid loss increased from 2.996 to 3.831 gm. per day.

There was no great increase of phosphorus in the urine with either subject, but in the feces the phosphorus elimination of the patient with goiter was increased to ten times the amount and that of the normal subject about 25 per cent. Since there was no such increase of nitrogen as of phosphorus outgo, Scholz believed that the latter was due to phosphate rather than nuclein metabolism. Richter¹² and Schiff³² confirmed these results. Anderson and Bergmann and Burger³³ found that with thyroid ingestion in the nonmyxedematous total phosphorus excretion was marked, amounting in the urine alone to 1 gm. above the amount ingested. Senator³⁴ confirmed these results. Burger's researches showed that the amount of ingested thyroid quantitatively governed the nitrogen and phosphorus pentoxid excretion. Roos in experiments on healthy dogs found that the administration of thyroid gland substance in large doses caused an increased phosphorus as well as sodium chlorid and nitrogen excretion. The increased phosphorus excretion continued longer than that of sodium chlorid. In a thyroidectomized dog, feeding of thyroid did not increase the phosphorus excretion to a greater degree than in the normal dog, but it remained considerably below normal. Roos noted evidence sustaining the idea that phosphorus as well as nitrogen assimilation requires the assistance of the secretory product of the thyroid.

Ord and White,³⁵ studying thyroid treatment in myxedema, noted a slight total increase in phosphorus metabolism. Richter found that the phosphorus excretion exceeded that of nitrogen. Schafer showed on white rats that the extent of increase of phosphorus excretion depended on the quantity of thyroid ingested, which had to be increased

31. Towles: *Am. Jour. Med. Sc.*, 1910, cxi, 100.

32. Schiff: *Ztschr. f. klin. Med.*, 1897, xxxiii (supplementary number), 284.

33. Burger: *Inaug. Diss.*, Halle, 1895.

34. Senator: *Berl. klin. Wchnschr.*, 1897, xxxiv, 109.

35. Ord and White: *Brit. Med. Jour.*, 1893, ii, 216.

beyond a certain point before any results were obtained. However, Scholz in his studies on the three cretins above referred to concluded that the phosphorus retention is considerable on small intake, and does not increase in proportion to intake.

The results with thyroid feeding following thyroparathyroidectomy or thyroidectomy alone, may vary even more. There may be a sub-normal elimination of phosphorus, a retention, or a return to normal metabolism or an increased phosphorus elimination. Underhill and Saiki¹⁸ observed a low output of phosphorus and a high output of purin nitrogen after the continued administration of large doses of thyroid tissue to dogs. Saccone³⁶ observed that the urinary phosphorus rose to three times the previous amount after removal from a dog of both the thyroids and parathyroids. The feeding of thyroiodin in addition to the normal diet reduced the excretion of phosphorus to the original low level. Roos showed that the administration of thyroid substance to a thyroidectomized dog did not increase the phosphorus elimination. After performing thyroidectomy in dogs, Ushenko³⁷ stated that the relation of the percentage of phosphorus to nitrogen in the urine first increased and later diminished. Similar results were obtained for ammonia. He concluded that the metabolism of phosphorus and nitrogen was acutely disturbed and that the synthetic processes were the ones mainly affected.

Magnus-Levy,¹⁹ discussing the metabolism of sulphur in exophthalmic goiter, says that nothing is known about its excretion either as to amount or its balance. The catabolism of sulphur, however, as shown by Daddi and Marchetti³⁸ varies as little from the normal as do the constituents of the nitrogen partition in protein metabolism. The excretion of sulphur after thyroid feeding of the nonmyxedematous frequently rises (Pfeiffer and Scholz³⁹ and Georgiewsky¹⁹), according to Burger,¹⁹ as high as 60 per cent., or much higher than the rise in nitrogen, though this result is not constant. Pfeiffer and Scholz found that the sulphur excretion rose to about the same extent as that of nitrogen, after thyroid feeding.

Sulphur excretion may parallel that of nitrogen or rise above it. Hirschstein⁴⁰ recently reported conclusions only of metabolism studies during long-continued thyroid medication, in which in a certain type of hypothyroidism, designated the asthenic, readily leading to great emaciation, there was a high excretion of sulphur, nitrogen, and phos-

36. Saccone: *Ann. di med. navale*, 1907, 13, i, 573.

37. Ushenko: *Russk. Vrach.*, 1913, 1751; *Chem. Abstr.*, 1913, vii, 3150.

38. Daddi and Marchetti: *La Clinica Moderna*, No. 1; *Biochem. Centralbl.*, 1904, ii, 752.

39. Pfeiffer and Scholz: *Oppenheimer's Handbuch der Biochemie der Menschen und der Tiere*, 1910, iii, Part 1, 294.

40. Hirschstein: *Med. Klin.*, 1914, x, 1569.

phorus, the sulphur excretion being especially high. Another type, designated plethoric hypothyroidism, is recognized by a high body resistance, the tissues showing no tendency to disintegration. Hirschstein determines by a preliminary trial which type predominates by thyroid feeding, or first by a high potassium diet, which he claims will cause a similar high excretion of sulphur, phosphorus, and nitrogen in the asthenic type, just as thyroid feeding does. He states that thyroid treatment in such patients is not advisable. The question arose whether these excreted end-products of protein metabolism were the results of tissue destruction or the washing out of residues stored in the body. The high sulphur and phosphorus excretion in some patients of the asthenic type, with great bodily wasting and susceptibility to intercurrent disease (tuberculosis), led him to believe that protein catabolism was the main factor. This author believes, however, that both forms are possible.

This study was carried out on a patient in the Jefferson Hospital, in the service of Dr. McCrae, to whom we are indebted for permission to study the case and for the clinical history, which is here given in part:

Clinical History.—Mrs. G. D., aged 28, white, was admitted to the Jefferson Hospital Aug. 6, 1913. Her general health had always been good. Menstruation was established at the age of 11 and was apparently normal in every respect until two years previous to her entrance it began to lessen in amount and duration. The previous year and one-half there had been amenorrhea. She had never been nervous until the onset of the present trouble. Her appetite always had been good, but for the previous four weeks it had been almost insatiable. The craving was mostly for bread and pastry. The bowels were regular. The present trouble began two years before. She noticed that her disposition had changed from an agreeable one to one markedly less so, that her temper flared up and she became irritated on the slightest provocation. These were the only symptoms apparent except for the beginning change in menstrual periods. Shortly afterward she noted a tremor of the hands, which had increased very little up to that time. In the previous year she noted that her eyes were becoming more prominent and in the previous three months she had noticed an increased size of her neck. On noticing this last symptom she consulted a physician, who treated her medically over a period of five weeks, with but slight improvement. During the medical treatment the patient received on three occasions hypodermic injections of pituitary extract and eight or nine days after each injection she became unconscious for periods of from twenty-four to seventy-two hours. She had headaches frequently and edema of ankles at times. She complained of dyspnea on slight exertion, but there was no dysphagia. In the previous six months the patient had gained considerable in body weight. Alopecia was noted of the hairy portions of the body. The patient was well nourished, with a most noticeable exophthalmos. The pulse was 110, the temperature 98.

Physical examination showed that on the neck there was an asymmetric enlargement of thyroid gland, more marked on the right than the left side. The enlargement began in the right side glands. There was no palpable thrill. The enlargement moves up on swallowing. The greatest circumference over the gland was $14\frac{3}{4}$ inches. The chest, lungs and heart sounds were normal. The

extremities were negative. The abdominal wall contained excessive amounts of fat.

The urinary examination was negative.

Blood examination on Aug. 15, 1913, showed hemoglobin 60 per cent., white cells 8,200, red cells 4,150,000, and color index 0.7 plus; the polymorphonuclears were 48 per cent., small lymphocytes 42 per cent., large lymphocytes 8 per cent., eosinophils 2 per cent. There was no reduced tolerance for glucose or fructose noted.

August 23 we began giving three lutein tablets daily to the patient. Bulimia continued. Examination of feces August 25 was negative. Wassermann examination resulted in positive three plus on September 5. On September 10, after mixed treatment, the patient showed a gain of 10 pounds the previous week. On the 11th she was given Roentgen-ray and thyroid treatment. On the 13th she was given pituitary treatment. On the 15th she was given 0.6 gm. salvarsan intravenously with no ill effects. On the 16th the weight indicated a loss of 6 pounds in the previous week. The patient stated that after the intravenous injection of salvarsan she felt a great deal more active mentally.

Blood examination, October 12, showed hemoglobin 91 per cent., red cells 5,950,000, color index 0.8, white cells 12,600.

An eye report of Aug. 11, 1913, showed vision of right eye 20/100, of left eye 20/200. The pupil diameter was 3.5 mm. The reactions to light, accommodation and convergence were normal. The muscle balance was normal, ocular movements were unimpaired, and the tension was normal. The eyeballs had undergone a proptosis of about 4 mm. in advance of the superior margin of the orbits. There was marked exophthalmos, so that the palpebral fissure could not be closed. Von Graefe's sign was present, as was also Stellwag's sign. Moebius' sign was absent. The right eye disk margins were clear and the vessels normal. There were no hemorrhages, and the fundus was negative. There was myopia of one-third diopter. The left eye mediums were clear, the disk margins were hazy on the nasal side, the cup was filled in, and the vessels were normal. The disk was slightly pale on the temporal side, and there was low myopia. The poor vision was due to the myopic condition of the eyes.

Roentgen examination on Aug. 13, 1913, showed the sella turcica and accessory sinuses normal. There was a calcareous deposit in the pineal gland.

The provisional diagnosis was goiter and pluriglandular disturbance.

PLAN AND METHOD OF STUDY

The patient was kept in a room in the Jefferson Hospital and under charge of a special nurse throughout the period of study. The purpose was to study the metabolism of the patient on a constant moderately high calcium diet, 1 gm., and to determine also the effect of the administration of both the thyroid and thymus gland substance. Both income and outgo of nitrogen, phosphorus, sulphur, calcium and magnesium were determined. The uniform diet and the amounts of each food given were based on the patient's choice during a preliminary day. The patient in all periods was placed on this uniform diet, which consisted of the foods given in Table 1, in addition 1 gm. of pure salt and 15 gm. of granulated sugar. There were also given each day bananas (scraped), 100 gm.; peaches (no juice), 100 gm.; tomatoes, 100 gm.; corn, 100 gm.; grape nuts, 50 gm.; potatoes (chips), 50 gm.; coffee, 200 c.c. and tea, 400 c.c.; both sampled daily. In order to reduce errors of sampling to a minimum, these foods were selected because of

the fact that they were low in calcium and nitrogen and yet gave variety to the diet. The details of food preparation and collection of excreta were carried out with the careful cooperation of the patient and of the hospital staff. The meat was prepared previous to the experiment, thoroughly mixed, boiled, and again thoroughly mixed, placed in glass jars, sterilized and kept in a frozen condition until used. Aliquot portions were taken for analysis.

TABLE 1.—ANALYSIS OF FOODS †

Sample	Daily Food Intake	Sample No.	N	P ₂ O ₅	MgO	CaO	S
Milk.....	100 c.c.	1	0.568	0.023	0.15
Milk.....	100 c.c.	2	0.568	Comp.	0.023	0.159
Milk.....	100 c.c.	3	0.568	0.219	0.024	0.157	Comp.
Milk.....	100 c.c.	4	0.583	0.025	0.162	0.025
Milk.....	100 c.c.	5	0.589	0.025	0.163
Cheese.....	50 gm.	1	2.054	0.033	0.504	Comp.
Cheese.....	50 gm.	2	2.136	Comp.	0.033	0.529
Cheese.....	50 gm.	3	2.272	0.521	0.03	0.486	Comp.
Cheese.....	50 gm.	4	2.3	0.03	0.463	0.081
Cheese.....	50 gm.	5	2.44	0.027	0.479
Butter....	50 gm.	2	3.546	0.509	0.081	0.129	0.07
Bread.....	200 gm. }						
Composite†.....	5	2.584	0.903	0.288	0.188	0.585
Meat (a).....	100 gm.	3a	1.266	0.521	0.037	0.022	Comp.
Meat (b).....	56 gm.	3b	1.308	0.475	0.037	0.026	0.102
City water.....	2,600 c.c.	0.04	0.035	0.029

* The milk and cheese were sampled and aliquot parts taken daily for period composites. Aliquot parts were again taken of these milk and cheese samples and composited into one sample each for both phosphorus and sulphur determinations. Aliquot parts of bread and butter were taken, which were composited into one sample. Patient began using meat 3b on Sept. 17, 1915. Proportionate aliquot parts of 3a and 3b were taken for sulphur, and for phosphorus in period 3.

† The daily intake consisted of (a) bananas (scrapped), 100 gm.; peaches (no juice), 100 gm.; tomatoes, 100 gm.; corn, 100 gm.; (b) grape nuts, 50 gm.; potato chips, 50 gm.; (c) coffee, 200 c.c.; tea, 400 c.c. (tea and coffee sampled daily and aliquots taken). Portions (a) and (c) were evaporated to dryness and composited with (b) comprising Composite 5.

‡ The quantities given are the total daily intake in grams.

The investigation extended over twenty-six days and consisted of five periods of five days' duration, except Period 1, which consisted of six days.

Urine was collected in exact twenty-four hour samples and kept in a refrigerator. Thymol was used as a preservative. The feces were separated by the use of carmin and kept in thymolized friction-top cans in a frozen condition until the end of the period, when they were thoroughly mixed for analysis.

All of the calcium except that in the urine was determined gravimetrically by McCrudden's methods.⁴¹ Urinary calcium was determined volumetrically by the same method. Nitrogen in the urine was estimated by the Kjeldahl-Gunning method. Phosphorus was determined by Neumann's method, gravimetrically. Sulphur in the urine was estimated by Benedict's method; in the food and feces, by a modification of Wolf and Osterberg's method.³² The analytical data of foods, urine and feces are given in Tables 1, 2 and 3.

The periods into which the experiment was divided were: 1, a fore-period, without any treatment; 2, a thyroid period, in which 6 grains of thyroid (Armour) were given daily, being increased to 9 grains each for the last two days, amounting to 36 grains in all; Period 3, a middle or after-period, in which no treatment was given; a thymus period

TABLE 2.—ANALYSIS OF FECES *

Period Number	Feces	N	P ₂ O ₅	MgO	CaO	S	Data
Foreperiod 1.....	443.5	9.49	4.981	1.393	5.034	0.553	Calculated to 5 day basis
Thyroid period 2.....	475.6	10.02	4.442	1.341	4.304	0.594	
Middle period 3.....	503.6	8.93	3.976	1.284	3.772	0.822	
Thymus period 4.....	521.1	9.64	4.328	1.345	3.871	0.745	
After period 5.....	544.5	9.16	4.116	1.242	3.91	0.808	Feces 5 of more liquid consistency

* The quantities given are the totals in grams for the respective periods.

(Period 4), in which 15 grains of thymus (Armour) were given daily, making a total of 75 grains, and an after-period (5), in which no treatment was given.

COMMENT

Some outstanding facts with regard to the metabolism in each of the periods of treatment will be outlined before going into a general discussion and comparison of the findings with regard to the individual elements concerned.

The point to be observed in Period 1, Table 4, with the patient receiving no treatment, is the loss of nitrogen, phosphorus, and magnesium, while calcium and sulphur are practically at a balance. The high daily loss of nitrogen amounts to 3.8 gm., or 37.03 per cent. of the intake. There is considerable loss of phosphorus, 0.399 gm., or 14.4 per cent. of the intake, while the loss of magnesium amounts to 0.025 gm., or 4.92 per cent.

41. McCrudden: Jour. Biol. Chem., 1910, vii, 83.

42. Wolf and Osterberg: Biochem. Ztschr., 1910, xxix, 429.

The calcium oxid and sulphur retentions announced to 0.01 and 0.023 gm., respectively. In this patient there was a loss of nitrogen somewhat over half as great as the gain Scholz¹ found in the case of his patient with goiter, who stored 7.437 gm. nitrogen daily without

TABLE 3.—ANALYSIS OF URINE *

Urine Number	Date	Vol., C.c.	N	P ₂ O ₅	MgO	CaO	S
Foreperiod 1 (no treatment)							
1.....	9/ 3	910	8.1	1.448	0.171	0.017	0.591
2.....	9/ 4	2,265	15.08	3.02	0.313	0.016	0.957
3.....	9/ 5	2,210	9.98	1.659	0.228	0.009	0.544
4.....	9/ 6	Lost					
5.....	9/ 7	2,187	10.25	2.14	0.271	0.024	0.675
6.....	9/ 8	3,374	15.58	2.614	0.295	0.013	0.983
Period 2, thyroid treatment							
7.....	9/ 9	2,980	13.2	2.319	0.26	0.024	0.77
8.....	9/10	2,131	7.82	1.323	0.152	0.016	0.472
9.....	9/11	2,825	9.81	1.91	0.189	0.017	0.696
10.....	9/12	2,521	13.1	2.468	0.269	0.023	0.828
11.....	9/13	1,895	7.64	1.318	0.189	0.016	0.476
Period 3 (no treatment)							
12.....	9/14	2,200	6.8	1.393	0.127	0.006	0.675
13....	9/15	1,615	6.42	1.142	0.101	0.018	0.466
14.....	9/16	1,800	7.9	1.37	0.139	0.018	0.52
15.....	9/17	1,948	10.76	1.715	0.218	0.024	0.742
16.....	9/18	1,535	8.16	1.044	0.159	0.023	0.715
Period 4, thymus treatment							
17.....	9/19	885	6.6	0.868	0.147	0.015	0.609
18.....	9/20	1,860	8.53	1.16	0.168	0.018	0.79
19.....	9/21	1,210	6.14	0.95	0.119	0.007	0.434
20.....	9/22	1,030	7.22	1.27	0.154	0.01	0.562
21.....	9/23	1,212	10.28	1.609	0.214	0.013	0.748
Period 5 (no treatment)							
22.....	9/24	1,610	8.06	1.456	0.181	0.018	0.565
23.....	9/25	1,975	7.7	1.132	0.174	0.016	0.633
24.....	9/26	1,735	6.82	0.906	0.14	0.015	0.455
25.....	9/27	2,168	7.53	1.065	0.186	0.029	0.498
26.....	9/28	1,310	6.53	0.982	0.144	0.013	0.43

* The quantities given are the totals in grams for each day.

treatment. The opposite condition obtains here. That sulphur is not lost with such a high daily excretion of nitrogen is unusual. Vermeiren²⁴ observed in myxedema a loss of 20 per cent. of nitrogen by

the feces, and Anderson⁴³ observed defective absorption as regards nitrogen and fat. In such cases the absorption improves with thyroid treatment.¹⁹ Improved absorption from the intestine was observed in Period 2 (Table 5) after thyroid administration. The urinary calcium excretion is unusually low, 15.9 mg. in twenty-four hours, or 1.54 per

TABLE 4.—PERIOD 1; BALANCE OF NITROGEN, PHOSPHORUS, MAGNESIUM, CALCIUM AND SULPHUR *

	N	P ₂ O ₅	MgO	CaO	S
Excretion, urine.....	11.8	2.176	0.256	0.016	0.752
Excretion, feces.....	2.28	0.996	0.279	1.006	0.117
Excretion, total.....	14.08	3.172	0.534	1.023	0.869
Ingestion, total.....	10.27	2.773	0.509	1.032	0.892
Retention or loss.....	-3.8	-0.399	-0.025	+0.01	+0.023
Per cent. of retention or loss.....	-37.03	-14.40	-4.92	+0.94	+2.57

* The quantities given are daily averages in grams.

cent., while the calcium in the feces is high, 97.8 per cent. of the total intake. Nitrogen in the feces was approximately three times the normal, being 22.2 per cent., indicating poor absorption. The condition of metabolism here, with high urinary losses, is such that there was a considerable amount of work for the kidneys to perform. The metabolism was below normal. The patient's weight remained constant at

TABLE 5.—PERIOD 2, THYROID TREATMENT; BALANCE OF NITROGEN, PHOSPHORUS, MAGNESIUM, CALCIUM AND SULPHUR *

	N	P ₂ O ₅	MgO	CaO	S
Excretion, urine.....	10.31	1.868	0.201	0.019	0.652
Excretion, feces.....	2	0.889	0.268	0.861	0.119
Excretion, total.....	12.32	2.756	0.57	0.88	0.771
Ingestion, total.....	10.1	2.773	0.502	1.002	0.892
Retention or loss.....	-2.22	0.017	0.032	0.122	0.121
Per cent. of retention or loss.....	-21.96	0.61	6.36	17.1	13.56

* The quantities given are daily averages in grams.

183 pounds, when not under medication. On August 24 her weight was 181 pounds, and on September 7 it was 183, indicating a gain of two pounds with metabolism below normal.

In Period 2, Table 5, 36 grains of thyroid gland, ingested in five

43. Anderson: *Hygica*, 1898, lx. 68; *Jahresb. ü. d. Fortschr. d. Thierchem.*, 1899, xxix. 427.

days, produced a marked effect on metabolism, causing a distinct increased retention over Period 1 of 15.07 per cent. nitrogen, 15.01 per cent. phosphorus pentoxid, 10.78 per cent. magnesium oxid, 16.16 per cent. calcium oxid and 10.99 per cent. sulphur. Nitrogen alone of all these elements remains negative at 21.96 per cent., or a daily loss of 2.22 gm. This agrees with Magnus-Levy's¹⁹ finding in myxedema.

Sulphur metabolism need not always parallel that of nitrogen. Magnus-Levy found the losses were greater during the beginning of the treatment. The nitrogen losses during the first nine days of his investigation were, respectively, 1.1, 0.3, 1, 2.7, 1.8, 3.3, 2.9, 1.6, and 2.9 gm., averaging 1.96 gm. The great daily variation in nitrogen losses is noticeable in the present instance. Phosphorus retention is 0.017 gm., or 0.61 per cent., being almost a balance. In case of calcium and sulphur there was a decided retention, amounting to 0.182 gm. and 0.121 gm., respectively, indicating for calcium, at least, a better absorption from the intestine. The same fact holds for nitrogen and calcium in the feces, which are 19.8 and 81.27 per cent., compared to 22.2 and 97.8 per cent., respectively, in Period 1. There was practically no change in calcium oxid excreted through the kidneys. The body weight now decreased to 177 pounds on September 17, which represented a considerable loss (at least six pounds) after the experiment began. While the volume of urine excreted in Period 1 was high, there now was an average increase of 293 c.c. (diuresis) (Table 3). This will be discussed more fully later. Incomplete data indicate that thyroid also increased the sodium chlorid excretion.

TABLE 6.—PERIOD 3, POSTTHYROID PERIOD; BALANCE OF NITROGEN, PHOSPHORUS, MAGNESIUM, CALCIUM AND SULPHUR *

	N	P ₂ O ₅	MgO	CaO	S
Excretion, urine.....	8.01	1.333	0.149	0.018	0.629
Excretion, feces.....	1.79	0.795	0.257	0.754	0.164
Excretion, total.....	9.80	2.128	0.406	0.773	0.793
Ingestion, total.....	10.25	2.770	0.5	1.021	0.892
Retention or loss.....	0.45	0.642	0.094	0.248	0.099
Per cent. of retention or loss.....	4.39	23.17	18.77	24.33	11.06

* The quantities given are daily averages in grams.

The nitrogen balance in Period 3 shows a retention of 0.48 gm., or 4.39 per cent. This indicates an increased retention of 26.35 per cent. over the preceding period. The stimulating effect of thyroid on metabolism continues and is greater in this than in the thyroid period. This is also true of phosphorus, in which the retention reached 23.7

per cent. The magnesium retention increased over the preceding period to 18.77 per cent.

The increase of calcium and sulphur was less in this period than in the preceding. However, magnesium and calcium in this period reach the maximum retention of 18.77 and 24.83 per cent., respectively, or 0.098 and 0.248 gm. This leaves 73.7 per cent. calcium oxid excreted through the feces, which in Period 1 contained 97.8 per cent. Urinary calcium does not vary any more than 0.55 per cent., or a mean of 7 mg. per day throughout the investigation. In this period, five to ten days following thyroid treatment, it is seen that the thyroid exerts its greatest effect on the metabolism of calcium and magnesium, which reaches its maximum quicker than metabolism of the other elements. The sulphur retention of 11.06 per cent. showed a slight decrease. Fifteen grains of thymus were administered daily, or a total of 75 grains for a period of five days.

TABLE 7.—PERIOD 4; EFFECT OF THYMUS TREATMENT ON NITROGEN, PHOSPHORUS, MAGNESIUM, CALCIUM AND SULPHUR RETENTION *

	N	P ₂ O ₅	MgO	CaO	S
Excretion, urine.....	7.75	1.171	0.161	0.013	0.619
Excretion, feces.....	1.93	0.866	0.269	0.776	0.140
Excretion, total.....	9.68	2.037	0.43	0.789	0.768
Ingestion, total.....	10.32	2.727	0.502	1.002	0.892
Retention or loss.....	0.63	0.69	0.072	0.216	0.124
Per cent. of retention or loss.....	6.15	25.3	14.31	21.5	13.85

* The quantities given are daily averages in grams.

The metabolism in Period 3 shows a retention of all elements, nitrogen being the lowest, 4.39 per cent. On administration of thymus gland (Period 4) the retention of nitrogen increases slightly, 1.76 per cent., or to 0.634 gm.; there was also a slightly increased retention of phosphorus and sulphur. However, magnesium oxid and calcium oxid retention decreased by 4.46 per cent. and 2.83 per cent., or the retention was 14.31 and 21.50 gm., respectively. The continuing effect of thyroid is not apparent in the magnesium and calcium metabolism; but this effect is shown in the slight increases in the metabolism of nitrogen, phosphorus and sulphur. That this is the lagging effect of thyroid stimulation, rather than the effect of thymus, appears probable. Blondel, as well as Tarrulli and Curatulo⁴⁴ claim that feeding of thymus causes increased nitrogen and phosphorus excretion.

44. Blondel, Tarulli and Curatulo: Biedl's Innere Sekretion. 1913, Part 1, 303.

In general, the results with thymus feeding have been negative. The urine excretion during this period decreased markedly to a daily mean of 1,239 c.c. The body weight of the patient also decreased 8 pounds from September 17 to the 24th, even though there was retention of all the elements, which is greatest relatively for phosphorus and calcium, being 25.30 and 21.50 per cent. respectively.

TABLE 8.—PERIOD 5; BALANCE OF NITROGEN, PHOSPHORUS, SULPHUR, CALCIUM AND MAGNESIUM IN THE POSTTHYMUS PERIOD

	N	P ₂ O ₅	MgO	CaO	S
Excretion, urine.....	7.33	1.108	0.165	0.018	0.520
Excretion, feces.....	1.83	0.823	0.248	0.782	0.162
Excretion, total.....	9.16	1.931	0.414	0.8	0.682
Ingestion, total.....	10.46	2.727	0.498	1.019	0.892
Retention or loss.....	1.3	0.796	0.085	0.219	0.21
Per cent. of retention or loss.....	12.45	29.19	16.96	21.47	23.56

* The quantities given are daily averages in grams.

TABLE 9.—RETENTION OR LOSS, PERCENTAGE

	1	2	3	4	5
N.....	-37.03	-21.96	4.89	6.15	12.45
P ₂ O ₅	-14.4	0.61	23.17	25.3	29.19
MgO.....	-4.92	6.36	18.77	14.31	16.96
CaO.....	0.94	17.1	24.33	21.5	21.47
S.....	2.57	13.56	11.06	13.85	23.56

TABLE 10.—RETENTION OR LOSS, ABSOLUTE, IN GRAMS

	1	2	3	4	5
N.....	-3.80	-2.22	0.45	0.63	1.3
P ₂ O ₅	-0.399	0.017	0.642	0.69	0.796
MgO.....	-0.025	0.032	0.094	0.072	0.085
CaO.....	0.01	0.182	0.248	0.216	0.219
S.....	0.023	0.121	0.099	0.124	0.21

In the postthymus period (Period 5) the retentions of the elements remained high, being at a maximum for the elements nitrogen, phosphorus and sulphur.

Tables 9 and 10 give the absolute and percentage retentions for all periods. It will be seen that the great increases in retention occurred

toward the left of the table, that is during the thyroid period (Period 2) or in the postthyroid period (Period 3). The increases in retention after Period 3 are gradual for all elements.

On the whole the retentions, both relative and absolute, are at their maximum in the postthymus period, sulphur 23.56 per cent., phosphorus 29.19 per cent., calcium 21.47 per cent., magnesium 16.96 per cent. (calcium and magnesium were highest in Period 3, 24.33 per cent. and 18.77 per cent., respectively), nitrogen 12.45 per cent. The absolute retentions occurred in the following order: nitrogen 1.3 gm., calcium 0.219 gm., sulphur 0.21 gm., phosphorus 0.796 gm., magnesium 0.085 gm. The percentage of retentions show there is a certain parallelism in metabolism for nitrogen and the mineral elements. Towles,⁴⁵ studying metabolism in exophthalmic goiter, has pointed out that there is often a parallelism between the nitrogen and calcium in health and disease, unless the calcium intake is very high. McCrudden and Fales⁴⁶ point out that this has been found for other elements, and that it holds for the retention of nitrogen and of the mineral elements in a normal body. Hoffström,⁴⁷ who studied the metabolism of a pregnant woman over a long period, also showed a similar retention of nitrogen and the other elements.

It will be noted that the maximum retentions of nitrogen, phosphorus and sulphur occurred in the final period, while the highest retentions for calcium and magnesium occurred in the postthyroid period; that is, with calcium and magnesium the maximum effects were reached earlier.

With regard to the influence of thymus administration, it will be noted that when this treatment was discontinued, there is a rise in retention in the case of all elements. Furthermore, in the cases in which the rise in retention is continuous, the retention increased to a greater extent when thymus was withdrawn than it had in the preceding period. That is, the thymus treatment apparently produced an effect distinguishable from and opposed to the continuing effect of the thyroid treatment. It appears to have exerted a depressing effect on the thyroid stimulation of metabolism. In view of the lack of data with regard to the effect of thymus administration on metabolism, the interpretation of these findings offers many difficulties. Falta,⁴⁸ on the basis of indirect evidence, suggests that probably the thymus gland belongs to the anabolic (retardative) group of ductless glands, as contrasted with the thyroid as a member of the catabolic or dissimilatory group.

45. Towles: *Am. Jour. Med. Sc.*, 1910, cxi, 100.

46. McCrudden and Fales: *THE ARCHIVES INT. MED.*, 1912, ix, 273.

47. Hoffström: *Skand. Arch. f. Physiol.*, 1910, xxiii, 326.

48. Falta, Bolaffio, and Tedesco: Cited by Biedl (65) Part 1, p. 164. Falta and Meyers: *The Ductless Glandular Diseases*, Philadelphia, 1915, p. 80.

Through the pioneer work of Hertoghe it has been shown clinically how frequently hypothyroidism occurs, causing various slight infiltrations now clinically recognized and relieved by thyroid medication.

Our knowledge of the purpose of the thymus gland in metabolism is obscure. However, in the last few years the observations of surgeons have added considerably to our knowledge. Swale Vincent⁴⁹ observes that the conception that the thymus is not altogether a lymph organ is gaining ground. A nutritive rôle has also been suggested for the thymus, it being a glandular organ rich in nucleoprotein.

Weil,⁵⁰ Hart and Nordmann,⁵¹ state that on the whole the verdict appears to be that the organ is not essential to life, even in quite young animals. It has long been thought that the human thymus reaches its greatest development at about the second year, and then begins to degenerate. But it was shown in the year 1890 by Waldeyer⁵² that even in advanced age a considerable amount of thymus tissue persists and probably maintains its function as does the thyroid. Zoja⁵³ had previously shown that the thymus persists till the age of puberty. Recently Hammar⁵⁴ has insisted that the organ continues to grow up to the period of puberty, and reaches its greatest development between the fourteenth and sixteenth years. Microscopic evidence shows that it functions still later, though losing in weight. A true atrophy of the parenchyma, with elimination of function, comes on at about 50 or 60 years of age. At this period the thyroid function also decreases (Hertoghe). It seems, then, that we must regard the thymus as an organ regularly present, and probably in an active functional condition up to the age of puberty, if not up to the menopause.

Gare and Capelle hold there is a reciprocal relation between the thyroid and thymus glands. The association between the thyroid and thymus glands⁵⁵ may be of importance in hyperthyroidism, in which a hyperplasia of the thymus has been reported to occur. Indeed, the degree of the latter has been directly related to the severity of exophthalmic goiter manifestations.⁵⁶ H. Matti reports that research and study of the literature show thymus with thyroid are directly concerned with the production of exophthalmic goiter. Thymus changes are directly coordinate with and parallel to changes in the thyroid.⁵⁷

49. Vincent: *Internal Secretion and the Ductless Glands*, London, 1912.

50. Weil: *Lyon Med.*, 1910, cxv, 847.

51. Hart and Nordmann: *Berl. klin. Wchnschr.*, 1910, xli, 814.

52. Waldeyer: *Verhandl. des 10 Internat. Med. Cong.*, Berlin, 1891, p. 15; cited by Vincent (Footnote 49) p. 357.

53. Zoja: Cited by Vincent (Footnote 49), p. 358.

54. Hammar: *Verhandl. d. Anat. Gesellsch. a. d. 19te Versammlung*, Geneva, 1905.

55. Hoskins: *Am. Jour. Med. Sc.*, 1911, cxli, 1349.

56. Gebele: *Beitr. z. klin. Chir.*, 1910, lxx, 20.

57. Matti: *Berl. klin. Wchnschr.*, 1914, li, 1365.

Tatum found that the thymus of rabbits atrophied after excision of the thyroid. A. Kocher⁵⁸ states that a tendency to tardy hyperplasia or tardy involution of the thymus is evident in nearly 50 per cent. of all cases of exophthalmic goiter. Halsted⁵⁹ in exophthalmic goiter twice found the thymus enlarged, with typical thymus symptoms predominating, and also found that 82 per cent. of the postmortem examinations showed thymus enlargement, while in those deaths due to heart failure after operation 95 per cent. showed thymus enlargement.⁶⁰ Gebele⁶¹ describes persistent thymus in exophthalmic goiter. The castration experiments of Marassini and Gellin⁶² point out that this operation gives rise to an enlargement of the thymus, and Squandrini⁶² believes that castration interferes with the normal involution of the gland. These experiments further point to some kind of internal secretion which ministers to the economy of the organism before the reproductive organs are fully developed. They believe that normally this internal secretion is provided by the testes or ovary after puberty, but if castration is perfected the thymus maintains its original structure and function.

Defective nutrition is caused in young dogs by extirpation of the thymus, the animals usually living about a year. Again, dilatation of the heart in such animals suggested that the thymus has an antagonistic action to the suprarenals.⁴⁹ The fatal effects of thymectomy in rats, as found by Klose and Marquini, could not be confirmed by Pappenheimer,⁶³ using controls of the same litter.

Soli⁶⁴ found changes in the development of bone in animals deprived of their thymus (supposedly deranged metabolism). Rabbits, if deprived of their thymus at a sufficiently early stage in their development, fail to develop their bony skeleton normally, while guinea-pigs and chickens respond less readily. Utterström,⁶⁵ after feeding thyroid to rabbits for weeks and months, concluded that two factors in hyperthyroidism affect the thymus: one is an indirect depressing effect, due to a disturbance in metabolism; the other is a direct stimulation, due to hyperthyroidism. Which predominates depends on the animal's constitution, conditions of the experiment and especially on the size of the thyroid dose.

58. Kocher: *Arch. f. klin. Chir.*, 1914, cv, 769, 832.

59. Halsted: *Bull. Johns Hopkins Hosp.*, 1914, xxv, 223.

60. Falta and Meyers in *The Ductless Glandular Diseases*, p. 45, say: "That long continued oversaturation of the body with the thyroid gland secretion may give rise to disturbances of the functions of the sexual glands is not at all remarkable, only the significance of the thymus hyperplasia is as yet unclear."

61. Gebele: *Beitr. z. klin. Chir.*, 1910, lxx, 20.

62. Marassini, Gellin and Squandrini: Cited by Vincent (Footnote 49), p. 365.

63. Pappenheimer: *Jour. Exper. Med.*, 1914, xix, 319.

64. Soli: *Arch. ital. biol.*, 1909, lii, 217; *Chem. Abstr.*, 1911, v, 2128.

65. Utterström: *Arch. de méd. exper. et d'anat. path.*, 1910, xxii, 550.

DIURESIS

A marked daily increase in urine volume (average volume 2,472 c.c.) occurred during thyroid treatment over that of the foreperiod (Period 1) (average volume 2,179 c.c.), which increase amounted to 293 c.c. The patient was on a constant water intake. The urine volume of Period 2 also exceeded that of the following period by 652 c.c. As shown by Rahel Hirsch (Table 13), in the work of Scholz,

TABLE 11.—DIURESIS DUE TO THYROID TREATMENT *

Period		Mean Temperature, F.	Mean Urine Volume, C.c.
No treatment.....	1	70.7	2,179
Thyroid.....	2	59.8	2,472
No treatment.....	3	67.0	1,820
Thymus.....	4	75.6	1,239
No treatment.....	5	61.2	1,759

* Period averages are given.

Richter and Bürger, there is a marked increased excretion of urine by persons on thyroid administration, except in the case of Gluzinski and Lemberger, in which there was a decrease. Scholz obtained an increase of 886 c.c.; Richter 219 c.c.; Bürger 122 c.c.; while Gluzinski and Lemberger obtained a decrease of 206 c.c. In our experiments, during thymus treatment the volume went down to 1,239 c.c., or 1,233 c.c. less than with thyroid, a variation of almost 100 per cent. While

TABLE 12.—URINE VOLUME DOES NOT VARY WITH TEMPERATURE

Period	Temp., F.	Urine Vol., C.c.
2.....	59.8	2,472
5.....	61.2	1,759
3.....	67.0	1,820
1.....	70.7	2,179
4.....	75.6	1,239

the greatest and lowest volume of urine occurred when the temperature was lowest, 59.8 F., and the highest 75.6 F., respectively, yet a variation of 1,233 c.c. of urine is considerable in a hospital in which temperatures are more constant and normal. Rearranging the urine volumes according to increase in temperature (Table 12) shows that the volume varies independently of temperature. Pointing out one instance will suffice. During the second warmest period (Period 1) the urine volume was

2,179 c.c., while in the warmest period (Period 4) this was 1,239 c.c. Magnus-Levy found that the urine increased somewhat during thyroid treatment in myxedema (hypothyroidism) on constant water intake. This, he says, is supposedly due to the disappearance of watery myxedematous deposit and other substances, and that the same holds for thyroid extract administered to the nonmyxedematous.

TABLE 13.—URINE VOLUME, QUOTED FROM RAHEL HIRSCH (OPPENHEIMER) *

O.c. Urine, Foreperiod	Author	C.c. Urine, Treatment Period
2,396	Scholz.....	3,282
1,120	Richter.....	1,339
1,419	Gluzinski and Lemberger.....	1,213
1,044	Bürger.....	1,166

* Oppenheimer: *Handbuch der Biochemie*, 1910, iii, Part 1, 294.

Friedleben⁶⁶ noticed diminished urine volume, decrease in amount of urea, increased appetite and that the metabolism was altered in thymectomized animals. During the thymus period in the case under investigation the volume of urine decreased to 1,239 c.c., and in the following period again rose to 1,759 c.c. (Table 11). Whether this marked decrease in volume is due to thymus ingested or is a coincidence has not been definitely determined.

TABLE 14.—VARIATION IN BODY WEIGHT

Date	Period	Weight, Pounds	Change, Pounds
8/24/14.....	...	181	
9/ 7/14.....	1	183	Gain 2
9/17/14.....	3	177	Lost 6
9/24/14.....	4, end	185	Gain 8
10/ 2/14.....	End of Exp.	174	Lost 11
5/15/15.....	...	183	
	Before illness	165	
7/17/16.....	...	185.5	

Various results had been obtained with thymus extract prepared in different ways. Gouin and Audouard⁶⁷ report increased activity of the kidney by using subcutaneous injection of glycerol extracts of thymus glands.

66. Friedleben: Cited from Oppenheimer's *Handbuch der Biochemie*, 1910, iii, Part 1, 335.

67. Gouin and Audouard: *Biedl's Innere Sekretion*, 1913, Ed. 2, Part 1, 302.

An outstanding fact in this case is the marked variation in body weight. The weights during the present investigation for the periods given are as shown in Table 14.

From August 24 to September 7 the patient gained two pounds in weight. Previous to September 1 the patient had been on thymus treatment. The clinical data indicate a slight edema on September 1: "Areas of thickening in the subcutaneous tissues. With these thickened areas there appeared a sense of constriction over upper chest and fugitive pains generally distributed." The kidneys at this time were eliminating large quantities of nitrogen (3.8 gm.) in excess of ingestion and also large amounts of water. With imperfect elimination of nitrogenous end-products from the tissues, due to poor or decreased oxidation, it is easily conceivable that there could occur a slight edema or myxedema, with retention of some water, and hence a slight increase in weight.

Thyroid treatment, however, caused increased water excretion and with its stimulating effect on metabolism brought about retention of other constituents. The loss in weight (6 pounds) is perhaps due chiefly to water. We can approximately calculate this from nitrogen loss and water excretions from September 7 to 17 (Table 14). During this period there was a loss of 6 pounds in body weight. The total loss of nitrogen from September 7 to 14 amounted to 22.5 gm. This, calculated to the basis of tissue equivalent (6.25 and 4.7, protein and tissue factors), gives 1.5 pounds tissue loss. Diuresis of 293 c.c. daily for five days (excess in Period 2 over Period 1) causes a loss of 1,465 c.c. This amounts to 1,487 gm., or 3.3 pounds (specific gravity 1.015). The loss of 3.3 pounds water with 1.5 pounds tissue loss accounts for 4.8 pounds. The actual loss was 6 pounds.

In Period 4 there is a distinct retention of all the elements, especially nitrogen. Urine excretion decreases in volume and gain in weight occurs. In our case this amounted to 8 pounds. This continues through the thymus period. Thymus may also cause a retention of water. The above gain occurred from September 17 to 24.

This gain in weight due to retention of nitrogen and of water can approximately be calculated from the urine volumes. The nitrogen retention in Period 3 was 0.45 gm. daily; that is, 0.90 gm. of nitrogen was retained up to September 19. Retention of nitrogen for Period 4 was 0.634 gm. daily, or a total of 3.17 gm. The total nitrogen retention for September 17 to 24 was 4.07 gm., equivalent to 0.3 pound of tissue built up. The mean daily urine excreted is not so readily approximated, but averaging the volumes for Periods 3 and 5 gives 1,790 c.c., which can be taken as the average. For the thymus period there would be a retention of 551 c.c. a day, which totals 2,755 c.c., or 2,796 gm. This is equivalent to 6.2 pounds, and with the 0.3 pound

of tissue, gives 6.5 pounds gain for September 17 to 24. The actual gain was 8 pounds.

It has been held that the fat in this disorder is readily oxidizable and perhaps the loss of 11 pounds (from September 24 to October 2, Table 14) is due partly to such oxidation. Agreeing with this is the fact that little or no sulphur loss occurs during the periods of great nitrogen losses (Periods 1 and 2). Hirschstein⁴⁰ found the sulphur loss was extraordinarily high when great emaciation occurs in hypothyroidism.

The Chittenden low-protein diet allows 0.12 gm. nitrogen per kilogram of body weight, which Siven was able to reduce to 0.08 gm. per kilogram. In our case the metabolism of nitrogen, as shown by the urinary nitrogen figured on the basis of kilograms of body weight, is low, indicating a low state of metabolism. Results on this basis are perhaps partly due to the presence of inactive adipose tissue. Table 15 illustrates this fact.

TABLE 15.—NITROGEN METABOLISM

Period	Weight		Mean N in Urine, Gm.	N per Kg. Body Weight, Gm.
	Lbs.	Kg.		
	165	74	11.8	0.16
1.....	183	83	11.8	0.14
4.....	185	84	7.33	0.09

The daily intake of 2,058 calories, corresponding to 25 calories per kilogram body weight, with choice of diet, also indicates a low energy metabolism.

NITROGEN METABOLISM

Table 16 points out the gradual decrease of nitrogen, absolute as well as relative, in the feces. Vermehren²⁴ observed in myxedema a loss of 20 per cent. of nitrogen by way of the feces and Anderson⁴³ observed defective absorption of nitrogen and fat, but states that with thyroid treatment absorption improved. The best absorption in our patient showed an improvement of 4.7 per cent. over Period 1. This occurred in the postthyroid period. The nitrogen in the urine decreased from 114.8 per cent. of the intake to 70.2 per cent., a difference of 44.6 per cent. There were less of the nitrogenous end-products given off and more nitrogen retained. Large increases in nitrogen retention occurred in Periods 3 and 5, following the thyroid and thymus periods, being respectively 26.35 and 6.30 per cent. The nitrogen metabolism went from a daily loss of 3.8 gm. to a retention of 5.1 gm., within a period of twenty-six days. The variation in nitrogen balance thus reached a maximum of 49.48 per cent. This increase in

nitrogen metabolism is further substantiated by the fact that the sulphur retention increased 20.99 per cent., phosphorus 43.59 per cent., while the mineral elements, calcium and magnesium, were retained in about the same amount as that of sulphur.

In the foreperiod and the thyroid period the nitrogen balance was negative, with a loss of 3.8 and 2.2 gm., respectively. Thyroid feeding stimulated nitrogen retention by 15 per cent., which increased to 26 per cent. in the postthyroid period (Period 3). There was a drop in the urinary excretion of nitrogen of 24 per cent., or 2.3 gm. This indicated increased retention. The nitrogen loss of 2.2 gm. changed in Period 3 to 0.05 gm. retention. This marked effect of nitrogen metabolism continues through the remaining periods. An interesting point to note is that the relative absorption through the intestine in both posttreatment periods (Periods 3 and 5) was the same, the absolute values for nitrogen in the feces being respectively 1.79 and 1.83 gm., a difference of 45 mg., while there was a difference of 0.22 gm. in the nitrogen ingested. Hence in these posttreatment periods it will be observed that the absorptive power of the intestine for nitrogen was not changed to any extent. This appears to hold also for sulphur and phosphorus (Tables 16, 19 and 22).

TABLE 16.—METABOLISM OF NITROGEN FOR ALL PERIODS
(RELATIVE AND ABSOLUTE) *

	Grams N, for All Periods					Percentage Based on Intake, for All Periods				
	1	2	3	4	5	1	2	3	4	5
Ingestion.....	10.27	10.1	10.25	10.32	10.46
In feces.....	2.28	2	1.79	1.93	1.83	22.2	19.8	17.4	18.6	17.5
In urine.....	11.8	10.31	8.01	7.75	7.33	114.8	102.2	78.2	75	70.2
Retention.....	-3.8	-2.22	0.45	0.63	1.3	-37.03	-21.96	4.39	6.15	12.45

* Maximum increased retention 49.48 per cent. (Period 5).

Daddi and Marchetti³⁸ found the utilization of nitrogen good in thyroid treatment of exophthalmic goiter, even though the stools were somewhat soft. We confirmed this on feces Composite 5, which were more liquid in consistency. Our data on the administration of thyroid confirm the observations of Magnus-Levy¹⁰ that the gradual effect of thyroid action on the nitrogenous exchange, both in myxedematous and nonmyxedematous, and its persistence after the administration has been stopped, are very noticeable; that while there are differences in the degree of reaction of individuals, this reaction is no more noticeable for the obese than for other individuals. The loss of nitrogen in the feces remained high (from 22.2 to 17.4 per cent.), that is, the variation

in absorption was slight, 4.8 per cent. (Table 17). There is in general, however, a gradual decrease in fecal nitrogen, being 0.28 and 0.49 gm., respectively during the thyroid and postthyroid periods. Fecal nitrogen, in the thymus and postthymus periods, increased over Period 3 (forethymus period) by 0.14 and 0.24 gm., respectively.

Corresponding with the continued effect of thyroid on metabolism, the urinary nitrogen shows a gradual decreased elimination from 11.8 gm. (Period 1) to 7.33 gm. (Period 5), or a difference of 4.47 gm., amounting to 44.6 per cent. The nitrogen excretion during the thyroid and postthyroid periods was, respectively, 1.48 and 3.80 gm. less than in the foreperiod (Period 1); during the thymus and postthymus

TABLE 17.—GRADUAL DECREASE OF NITROGEN IN URINE AND FECES
(RELATIVE AND ABSOLUTE)

Period	N Intake, Gm.	N in Urine, Gm.	N in Urine, per Cent.	N in Feces, Gm.	N in Feces, per Cent.
1.....	10.27	11.8	114.8	2.23	22.2
2.....	10.1	10.31	102.2	2	19.8
3.....	10.25	8.01	78.2	1.79	17.4
4.....	10.32	7.75	75	1.93	18.6
5.....	10.46	7.33	70.2	1.83	17.5

TABLE 18.—MAXIMUM VARIATION IN ABSORPTION, EXCRETION AND RETENTION

	Absorption	Excretion, Urine	Retention	Period
N.....	4.8	44.6	49.48	5
P ₂ O ₅	7.3	37.9	43.59	5
MgO.....	5	20.6	23.69	3
S.....	5.3	26	20.99	5
CaO.....	24.1	0.57	23.39	3

periods, 4.05 and 4.47 gm. less than in Period 1, indicating that during both treatment with thyroid and thymus there was a more favorable nitrogen balance.

Table 18 is interesting because of several facts brought out. The variation in absorption from the intestine for all elements is fairly constant, approximating 5 per cent. Phosphorus runs slightly higher. Calcium, while constant in the urine, varies up to 24.1 per cent. in the feces and must be excreted by this channel. The retention of the other four constituents is indicated by the urine content. Table 18 shows that this exceeds 20 per cent. for all (except calcium being

greatest for nitrogen and phosphorus, respectively). It should be observed that the maximum increased retention was about the same for calcium and magnesium and occurred earlier (Period 3) than for the elements (nitrogen, phosphorus and sulphur) concerned in the metabolism of protein (Period 5), which was respectively 49.48, 43.59 and 20.99 per cent. Thus calcium and magnesium metabolism appear to be affected differently by thyroid stimulation than that of nitrogen, phosphorus and sulphur.

PHOSPHORUS METABOLISM

There was a fairly progressive decrease in the excretion of phosphorus by way of the intestines during and after thyroid treatment. The excretion of the feces during thymus feeding increased somewhat, as it also did for nitrogen. The lowest excretion in the feces occurred following thyroid action. In the next two periods, Periods 4 and 5,

TABLE 19.—METABOLISM OF PHOSPHORUS IN ALL PERIODS, RELATIVE AND ABSOLUTE AMOUNTS (PHOSPHORUS PENTOXID) *

	Phosphorus in All Periods, Gm.					Phosphorus in All Periods, per Cent.				
	1	2	3	4	5	1	2	3	4	5
Ingestion.....	2.773	2.773	2.770	2.727	2.727
In feces.....	0.906	0.889	0.795	0.866	0.823	35.9	32.1	28.6	31.7	30.1
In urine.....	2.176	1.868	1.333	1.171	1.108	78.5	67.4	42.8	42.8	40.6
Loss or retention...	-0.399	0.017	0.642	0.60	0.796	-14.4	0.61	23.17	25.3	29.19

* Maximum retention 43.59 per cent. (Period 5).

there was a slight rise, but all variations were within the narrow limits of 7.3 per cent. Thus, it is seen that there was no marked increase in phosphorus metabolism with excretion through the bowel, such as Scholz¹⁹ observed in his case.

The progressive decrease of phosphorus excretion in the urine is noticeable, being from 2.18 to 1.11 gm., or a difference of 1.07 gm. (40.6 per cent.). Thyroid action caused a decreased excretion of 0.31 gm. and thymus 0.16 gm. over the preceding period in each case. This extended also into the postthyroid and postthymus periods, being 0.54 gm. and 0.06 gm., respectively. The maximum retention was 43.59 per cent. in Period 5.

MAGNESIUM METABOLISM

There was not over 5 per cent. variation in absorption of magnesium oxid from the intestine. A variation from 54.8 (Period 1) to 49.8 (Period 5), per cent. occurred. The absorption from the feces during thyroid and thymus action was practically the same, differing

only by 0.3 per cent. A marked effect of treatment on magnesium metabolism is seen from the urinary data. Excretion of magnesium oxid varied in Period 1 from 0.256 gm. to 0.149 gm. (Period 3), or from 50.4 to 29.8 per cent. The lowest excretion is caused by the continuing thyroid stimulation. The greatest retention occurs here (18.77 per cent.). The excretion rises slightly in Period 4 during thymus administration and also in Period 5 (33.06 per cent.). The maximum retention occurs in Period 5 (16.96 per cent.). This is an increased retention after the experiment began of 23.69 per cent. The absolute values for magnesium oxid retention in any period are small, being less than 100 mg.

TABLE 20.—METABOLISM OF MAGNESIUM IN ALL PERIODS
(RELATIVE AND ABSOLUTE) *

	As MgO, Gm.					As MgO, per Cent.				
	1	2	3	4	5	1	2	3	4	5
Ingestion.....	0.509	0.502	0.5	0.502	0.498
In feces.....	0.270	0.268	0.257	0.269	0.248	51.8	53.4	51.4	53.7	49.8
In urine.....	0.256	0.202	0.149	0.161	0.165	50.4	40.3	29.8	32.01	33.03
Loss or retention...	-0.025	0.032	0.034	0.072	0.085	-4.92	6.36	18.77	14.31	16.96

* Maximum retention 23.69 per cent. (Period 3).

CALCIUM METABOLISM

In the first two periods there is apparently a condition of depressed metabolism with loss of magnesium, phosphorus and nitrogen, calcium and sulphur being at a balance. The kidneys functionated but slightly in calcium metabolism, excreting 0.420 gm. in twenty-five days (from 12 to 18 mg. daily). This is less than 2 per cent. of the ingested calcium. Secchi⁶⁸ found for a man 70 years old that the lowest urinary excretion was 9.4 per cent. on a high calcium diet (3.65 gm. per day). The calcium eliminated in the foreperiod by way of the intestines in our patient was 97.7 per cent. of the intake.

During thyroid treatment absorption improved. Calcium oxid in the feces decreased to 81.2 per cent., or 0.146 gm. The least calcium oxid eliminated by way of the feces (73.7 per cent. or 0.754 gm.) occurred in the postthyroid period (Period 3).

The calcium oxid elimination in the feces during twenty-five days varied in the forethyroid period (Period 1) from 97.8 to 73.7 (Period 3) and was 76.6 per cent. at the close of the experiment. Secchi, working on normal persons, found from 40 to 60 per cent. of the calcium eliminated in the feces. Thus in this patient there was appar-

68. Secchi: Biochem. Ztschr., 1914, lxxvi, 156.

ently a deficient elimination and poor absorption of calcium from the intestine. An improvement in absorption of 16.6 per cent. occurred during thyroid administration, which increased in the postthyroid period (Period 3) to 24.1 per cent. The metabolism continued at a slightly lower level (2.9 to 3.8 per cent.) during the thymus and post-thymus periods. That is, calcium metabolism remained practically the same in the last two periods. Bergeim, Stewart and Hawk⁶⁹ in studying the metabolism of a case after thyroparathyroidectomy, also found low calcium in the urine (1/121 of that in the feces). McCrudden and Fales⁷⁰ found in a normal boy a retention of 17.1 per cent. calcium oxid per day of 2.5 gm. ingested, while one fifth of the excreted calcium occurred by way of the urine. Sherman, Mettler and Sinclair⁷¹ in their experiments report that calcium in the urine varied from 3.9 per cent. to 23.7 per cent. Determann⁷² states that phos-

TABLE 21.—METABOLISM OF CALCIUM (CALCIUM OXID) IN ALL PERIODS
(RELATIVE AND ABSOLUTE) *

	Calcium Oxid, Gm.					Calcium Oxid, per Cent.				
	1	2	3	4	5	1	2	3	4	5
Ingestion.....	1.032	1.062	1.021	1.002	1.019
In feces.....	1.007	0.861	0.754	0.776	0.782	97.8	81.2	73.7	77.5	76.6
In urine.....	0.016	0.019	0.018	0.013	0.018	1.54	1.81	1.79	1.24	1.78
Retention.....	0.01	0.182	0.248	0.216	0.219	0.04	17.1	24.33	21.5	21.47

* Maximum retention 23.39 per cent. (Period 3).

phorus and calcium excretion into the intestine is increased in exophthalmic goiter during thyroid treatment. Results obtained on the patient discussed above do not bear this out and do not confirm the results obtained by Falta, Tedesco and Bolaffio,⁴⁸ who found on thyroidectomized dogs no diminution in the metabolism of the mineral salts in the first days of hunger. There appeared, however, they report, to be a decreased excretion of sodium chlorid, also calcium, phosphorus and magnesium in the urine while on the administration of thyroid gland there was a rise in the calcium and phosphorus in the feces and of magnesium in the urine.

Further work⁶⁸ indicated that while in young children there is a retention of calcium in the normal adult there is a tendency for a calcium balance or equilibrium on varied diets containing from 0.4 to

69. Bergeim, Stewart, and Hawk: Jour. Exper. Med., 1914, xx, 225.

70. McCrudden and Fales: THE ARCHIVES INT. MED., 1912, ix, 287.

71. Sherman, Mettler and Sinclair: U. S. Dept. Agr. Bull. No. 227, 1910, O. E. S., p. 38.

72. Determann: Verdauung u. Stoffwechsel-Krankheiten, 1914, v, 60.

1.5 gm. calcium. Schabad,⁷³ among numerous calcium balance experiments in rickets, found an increased calcium excretion through the feces in the progressive stage of the disease; the calcium excretion through the urine was subnormal, but during convalescence above normal.

SULPHUR METABOLISM

The periods immediately following thyroid and thymus feeding, Periods 3 and 5, respectively, showed an increase within narrow limits in sulphur elimination through the feces (5.1 per cent., 0.048 gm., and 1.4 per cent., 0.045 gm.).

TABLE 22.—METABOLISM OF SULPHUR IN ALL PERIODS
(RELATIVE AND ABSOLUTE) *

	Sulphur, Gm.					Sulphur, per Cent.				
	1	2	3	4	5	1	2	3	4	5
Ingestion.....	0.892	0.892	0.892	0.892	0.892
In feces.....	0.117	0.119	0.164	0.149	0.162	13.03	13.3	18.4	16.7	18.1
In urine.....	0.752	0.652	0.629	0.610	0.52	84.4	73	70.5	69.4	58.4
Retention.....	0.023	0.121	0.099	0.124	0.21	2.57	13.56	11.06	13.85	23.56

* Maximum retention 20.99 per cent. (Period 5).

The excretion of sulphur by way of the urine underwent a diminution during the posttreatment periods. (Periods 3 and 5) of 2.5 per cent. and 11.0 per cent. Thyroid and thymus administration had slight effect on the excretion of sulphur in the feces, except that in the post-thyroid period (Period 3) sulphur excretion went up slightly, though less than 5 per cent., and remained near this level. In the urine there was a gradually decreasing excretion of sulphur from 84.4 per cent. (Period 1) to 58.4 per cent. (Period 5), a difference of 26 per cent. (0.232 gm. sulphur). The sulphur metabolism shows certain peculiarities. In the first place, in Period 1 there is no loss of sulphur such as occurred for phosphorus and nitrogen. The retention during the thyroid and thymus periods is approximately the same. There was only 26 mg. more sulphur metabolized during the thymus feeding. Decreased absorption occurred during the postthyroid period (Period 3), while in the postthymus period (Period 5) there was a considerable increase in metabolism, retention going from 0.124 gm. to 0.210 gm., or from 13.85 per cent. to 23.56 per cent. In the urine there was a gradual decrease from 0.752 to 0.520 gm., or a difference of 0.232 gm. from Period 1 to Period 5, amounting to 26 per cent. The administration of thyroid and thymus caused no rise of sulphur in the urine,

73. Schabad: Arch. f. Kinderheilk., 1910, liii, 380.

as occurred in feces. The retention was considerable in both treatment periods, 0.121 gm. in Period 2 and 0.124 gm. in Period 4, respectively, but greatest in Period 5, a total of 0.210 gm. (23.56 per cent.). Thus the sulphur excretion offers no suggestion of tissue disintegration.

Urinary Indican: The daily output of indican in the urine was determined by Jolle's colorimetric method. The average daily excretion of indican for each of the periods of study was as follows:

Period	Indican, Mg.
Foreperiod	25.2
Thyroid	12.6
Postthyroid	9.0
Thymus	10.0
Postthymus	4.4

It will be noticed that following thyroid treatment and coincident with improvement in nitrogen balance and in the condition of the patient there was a progressive decrease of urinary indican excretion. This may indicate decreased putrefaction, as it is associated with improved absorption of the food elements. The slight increase on thymus administration confirms certain work by Moraczewski, who found that the ingestion of thymus and certain other glandular tissues led to an increase in indican excretion.

SUMMARY AND CONCLUSIONS

A study was made of the metabolism of nitrogen, phosphorus, sulphur, calcium and magnesium on a patient with exophthalmic goiter, with apparently a slight hypothyroidism, and responding readily to treatment. The study was made in five periods of five days each, including periods of thyroid and thymus treatment.

In the preliminary period without treatment a marked disturbance of metabolism was noted, with pronounced losses of nitrogen, phosphorus, and magnesium and a practical balance of calcium and sulphur. The loss of nitrogen by the feces was much greater than that of an average normal person.

Thyroid treatment markedly stimulated the metabolism of all elements determined, this stimulation continuing long after treatment was stopped. Considerable retention of all elements was brought about, the maximum effect being reached sooner in the case of calcium and magnesium than in the case of nitrogen, sulphur and phosphorus. The retentions of the former reached their maximum in the third (postthyroid) period, while the latter showed a progressive increase in retention to the end of the experiment.

Slightly better intestinal absorption of nitrogen followed treatment, although the loss of nitrogen by the feces continued high. The intestinal absorption of other elements, with the exception of calcium,

varied but slightly. The urinary excretions of all elements except calcium markedly decreased after thyroid treatment, corresponding with the retention of these elements.

A retention of calcium was brought about, this reaching a maximum of 24.33 per cent. in the postthyroid period. The urinary calcium excretion was extremely low (2 per cent. of the intake) and continued so. The excretion of this element by the feces was markedly diminished, indicating better intestinal absorption.

The effect of thymus administration on the metabolism was less marked than that of the thyroid, but appeared to be distinct. In the thymus period the retention of all elements was depressed. When thymus administration ceased, the rate of retention for all elements immediately increased. Thus thymus treatment appeared to depress the stimulating effect of the thyroid on metabolism, which supports the view of a possible antagonistic action of these glands, such as has been suggested by others on the basis of indirect evidence.

The administration of thyroid caused diuresis immediately. Thymus treatment had the opposite effect, leading to a retention of water, with marked decrease in urine volumes (from 2,472 to 1,239 c.c.) on constant water ingestion.

The weight of the patient decreased on thyroid treatment and increased after withdrawal and on thymus administration. The variations (from 6 to 8 pounds) were apparently due in part to loss or gain of nitrogenous tissue constituents, but in the main to loss of water on thyroid treatment and retention on its discontinuance or on thymus treatment.

Following thyroid treatment there was a progressive decrease in urinary indican excretion. This may indicate lessened intestinal putrefaction.

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THE RELATION OF CHANGES IN THE FORM OF THE VENTRICULAR COMPLEX OF THE ELEC- TROCARDIOGRAM TO FUNCTIONAL CHANGES IN THE HEART *

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Constancy of form is one of the most striking characteristics of electrocardiograms obtained at various times from the same individual. Any change in form is therefore of interest, as it indicates some alteration in the passage of the impulse of contraction through the heart or some change in the manner of the muscular contraction. Changes in heart rate and in the force of contraction are not, as a rule, accompanied by definite alterations in the form of the electrocardiogram.

The ventricular portion of the electrocardiogram is composed of a series of waves and is initiated by a group of three waves, the so-called Q, R, S group. Of these, only the R wave is constant in normal individuals in records obtained by the three leads of Einthoven. There are at present differences of opinion as to the functional activity of the ventricles responsible for this group of waves. Without taking up the various points in this controversy, it may be said that the evidence is in favor of the hypothesis that it is the passage of the impulse through the ventricles rather than the actual muscular contraction which gives rise to this part of the electrocardiogram and initiates the ventricular complex. As Einthoven¹ has suggested this Q, R, S group deserves a closer examination than has been hitherto given to it in clinical electrocardiography, as it shows the path by which the excitation wave is conducted from the auricles to all parts of the ventricular walls. It is to changes in this initial part of the ventricular electrocardiogram that attention is directed in this paper.

Before discussing the type of change to be described, it is necessary to consider several well-defined abnormalities of the ventricular complex which are frequently encountered in clinical electrocardiograms, and which are well understood, because they have been repeatedly reproduced under experimental conditions. The commonest of these is that caused by the passage of impulses arising in some abnormal point in the ventricles, the so-called ectopic stimuli, which give rise

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1. Einthoven: Different Forms of the Human Electrocardiogram and Their Significance, *Lancet*, London, 1912, i, 853.

to ventricular premature contractions or extrasystoles. When this occurs the impulse passes through the ventricles in abnormal directions, yielding a ventricular complex which is, as a rule, much deformed.

Another well-defined abnormality of the ventricular complex is caused when an impulse which reaches the ventricles by the usual path is hindered in its passage throughout the ventricles by a derangement of one of the branches of the conducting system which should convey the impulse either to the right or to the left ventricle. Such a condition of bundle-branch block has been produced in animals by cutting one or the other of the main branches of the conducting system. This procedure is followed by a great change in the form of the electrocardiogram, as first described by Eppinger and Rothberger.² Electrocardiograms similar to those obtained after this experimental procedure have been obtained from patients whose hearts have later shown, on histologic examination, a lesion of one or the other of the main branches of the conducting system. A sufficient number of cases have been studied to justify the diagnosis of the lesion from the type of the electrocardiogram. Carter,³ who reported twenty-two cases of bundle-branch block, has pointed out the requirements of the form necessary to establish the diagnosis. The initial Q, R, S group of the ventricular complex exceeds the normal time 0.1 second; the waves are large, of bizarre forms, and the final deflection T is directed oppositely to the initial ventricular wave.

Changes in the distribution of muscle mass between the two ventricles, as occurs in cardiac hypertrophy, also leads to alterations in the form of the electrocardiograms, which is especially noticeable when the records obtained by the three usual leads are compared with one another. These changes have been recently demonstrated experimentally by Fraser.⁴ They are especially noteworthy in cases of congenital malformation of the heart. That the marked changes in the form of the electrocardiogram which occur in this condition are dependent on the abnormal distribution of the muscle mass between the two ventricles has been clearly demonstrated recently in our laboratory by McCulloch.⁵ One other change in the form of the electrocardiogram remains to be mentioned, which is frequently encountered clinically, namely, alterations in the size or direction of the final wave of the complex, the so-called T wave. This wave, which is normally a long, well-defined upwardly directed wave, may become diminished

2. Eppinger and Rothberger: Ueber die Folgen der Durchschneidung der Tawaraschen Schenkel des Reizleitungssystems, *Ztschr. f. klin. Med.*, 1910, lxx, 1.

3. Carter: Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle, *THE ARCHIVES INT. MED.*, 1914, xiii, 893.

4. Fraser: Changes in the Electrocardiograms Accompanying Experimental Changes in the Rabbit's Heart, *Jour. Exper. Med.*, 1915, xxii, 292.

5. McCulloch: *Am. Jour. Dis. Child.*, 1916, xii, 30.

in size, disappear or become inverted. Such a change is frequently observed in heart disease, especially when the myocardium is damaged. Kraus and Nicolai⁶ have laid stress on the inverted or negative T wave as an indication of myocardial weakness, and probably all who have made use of the electrocardiogram in the study of clinical material will agree that this change frequently accompanies other signs of myocardial disease. The fact, however, that such a change takes place in the T wave when digitalis is administered, as pointed out by Cohn, Fraser and Jamieson,⁷ renders its significance uncertain as an indication of myocardial weakness. It is mentioned here as being the one change in form of the ventricular complex which has been hitherto recognized as giving evidence as to the functional efficiency of the heart muscle.

The object of the present paper is to discuss a series of records which show changes in the form of the ventricular electrocardiogram differing from those that have been mentioned. These changes consist in alterations in the form of the Q, R, S group which are apparently dependent on a functional derangement of the ventricles, hindering the normal spread of the impulse of contraction. The spread of the impulse is hindered in some cases because the conducting system of the ventricles has not had a sufficient time to recover from the effects of an impulse that has just caused a ventricular contraction, while in other cases the recovery of the intraventricular conduction is abnormally delayed, so that the impulse spreads through the ventricles properly only after a prolonged period of ventricular rest. In some instances in which a prolonged rest does not occur the electrocardiogram is of a form which indicates that the proper spread of the impulse through the ventricles is constantly lacking. Changes in form of the complexes have been observed to occur from time to time parallel to the clinical course of cardiac cases. A consideration of these changes indicates that the electrocardiographic method may demonstrate functional deficiency of the conducting system in the ventricles and in this way be a means of revealing diminished functional capacity of the ventricles.

The records have been obtained by means of the Edelman type of string galvanometer. In all instances the tension of the string has been so adjusted that the passage of two millivolts through it, with the patient in the circuit, results in a deflection on the record of two centimeters. Only those records have been used in which this adjustment did not render the string sufficiently slack to cause any marked fling,

6. Kraus and Nicolai: *Das Elektrokardiogram*, Leipzig, 1910, p. 278.

7. Cohn, Fraser and Jamieson: *The Influence of Digitalis on the T Wave of the Human Electrocardiogram*, *Jour. Exper. Med.*, 1915, xxi, 593.

which results in a definite deformity of the curves. Omitting this precaution leads to striking errors. In lettering the curves the single letter R is used to mark the Q, R, S group.

CASE 1.—J. B., a man, 42 years of age, had been aware of an irregularity of the pulse since boyhood. Except for a heightened blood pressure (systolic 148 mm. of mercury, diastolic 95), moderate cardiac enlargement and a trace of albumin in the urine, he gave no signs of disease. He had never had a serious acute illness, and his only excess had been very constant hard work as a lawyer. His life had always been one of unrestricted activity. An examination was undertaken only as a means of determining the type of cardiac arrhythmia. Electrocardiograms (Fig. 1) revealed a sino-auricular block, a complete cardiac cycle being omitted every few beats. The arrhythmia was complicated, however, by the occurrence of an idioventricular beat, always occurring near the end of the long pause caused by the missed beat and immediately before the auricular contraction which initiated the restoration of the regular rhythm. This idioventricular beat yielded a complex practically identical with that of the normal beats, indicating that it arose in the junctional tissues before the division of the conducting system, and that the impulse spread through the ventricles in a normal manner.

The special interest in this record centers on the complexes yielded by the ventricular responses to the auricular contractions which occur immediately after the onset of the idioventricular contractions. The records furnish twenty-five examples of this combination. The electrocardiograms show that the ventricular responses to these auricular contractions vary with the time that elapses between the onset of the idioventricular beats and the auricular contractions. When this time is less than 0.15 of a second, usually no ventricular response follows the auricular contraction. As this time lengthens the ventricles respond, but when it is only a little longer than 0.15 of a second, the response is abnormal, as indicated by a prolonged auriculoventricular conduction time and by a markedly deformed ventricular complex.

The longer the time between the onset of the idioventricular contraction and the following auricular contraction, the shorter becomes the auriculoventricular conduction time and the nearer to the normal becomes the form of the ventricular complex. The more abnormal ventricular complexes show a prolongation of the time occupied by the Q, R, S group, which distinctly exceeds the normal time of 0.1 of a second. Both the ascent and descent of the R wave is more gradual than normally and there is a blunt, notched, or broken apex to the R wave, which is often distinctly diminished in height. The complexes are those to which Lewis⁸ has applied the term "aberrant."

These changes in the ventricular complexes of the electrocardiogram are interpreted as follows: At times the impulse from the auricular contraction reaches the ventricles when they are still in

8. Lewis: Observations on Disorders of the Heart's Action. Heart. 1912. iii, 279.

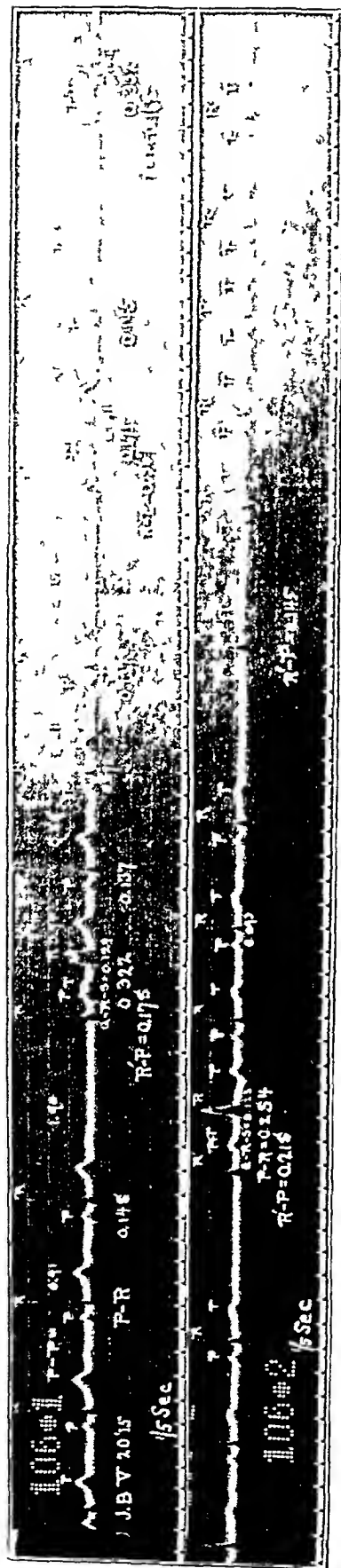


Fig. 1 (Case 1).—Sino-auricular block, with idioventricular contractions. The abnormal ventricular complexes are yielded by contractions which occur before the ventricles have recovered from a previous contraction.

the refractory phase, and so no ventricular response results. Usually the impulse reaches the ventricles when they have only partly recovered, and the conduction through the ventricles is depressed under these conditions, the impulse is delayed in part of the usual course, or follows an abnormal course, being blocked along some of its usual paths. Thus the intraventricular conduction apparently shows the same depression as is present in the auriculoventricular conducting system. The prolonged auriculoventricular conduction time is in part responsible for the degree of recovery which takes place in the ventricles, as this adds to the time between the idioventricular contraction and the ventricular contraction which follows.

The electrocardiograms of this case illustrate the changes in the form of the ventricular complex which are caused by functional derangement of the ventricles, when a contraction occurs before the ventricles have fully recovered from a previous contraction. They indicate also that the degree of abnormality of the complex parallels the degree of depression of the intraventricular conduction.

CASE 2.—S. B., a woman of 63 years, suffered from atrophic cirrhosis of the liver, chronic myocarditis and chronic valvular cardiac disease (mitral insufficiency). On May 2, 1915, when the first record was made, she was cyanotic, markedly dyspneic, and there was general anasarca. The heart was much enlarged, cardiac dulness extending 18.5 cm. to the left of the midsternal line, and besides the systolic murmur in the apex region there was a pericardial friction rub. The heart was beating at a rate of 87 per minute, and the systolic blood pressure was 110 mm. of mercury, the diastolic 65 mm.

The electrocardiograms (Fig. 2) are very abnormal in form. The Q, R, S group is composed of a series of waves, none of which resemble those of the normal electrocardiogram. The period of time occupied by the occurrence of this group of waves is distinctly longer than the normal 0.1 of a second.

On May 18, when electrocardiograms were again obtained (Fig. 3), the patient was much improved. The dyspnea, cyanosis and edema were distinctly less. The systolic blood pressure had risen from 110 to 120 mm. of mercury without change in the diastolic pressure. The heart rate was 82 per minute. The electrocardiograms show an arrhythmia caused by premature contractions of auricular, nodal and ventricular origin. There is a distinct change in the form of all ventricular complexes as compared with those seen in Figure 2. The most striking feature of the record is the change in the form of the ventricular complexes which occur after a period of increased ventricular rest. This change is seen after the compensatory pause following premature ventricular beats and when premature auricular beats are blocked. Under these conditions the ventricular complexes are much more nearly normal in form.

This case illustrates that changes in the form of the ventricular complexes may occur with improvement of the cardiac efficiency, as evidenced by the clinical improvement, and with increased periods of ventricular rest. The usual diastolic pause between the regular beats was not long enough to allow the intraventricular conduction to recover sufficiently to allow the impulse to pass normally. This case is, therefore, an example of those in which the recovery of the intra-



Fig. 2 (Case 2).—First record, May 2, 1915. Form of ventricular complexes abnormal in all leads. The Q, R, S time is prolonged; P-R time normal. The patient showed signs of marked cardiac decompensation.

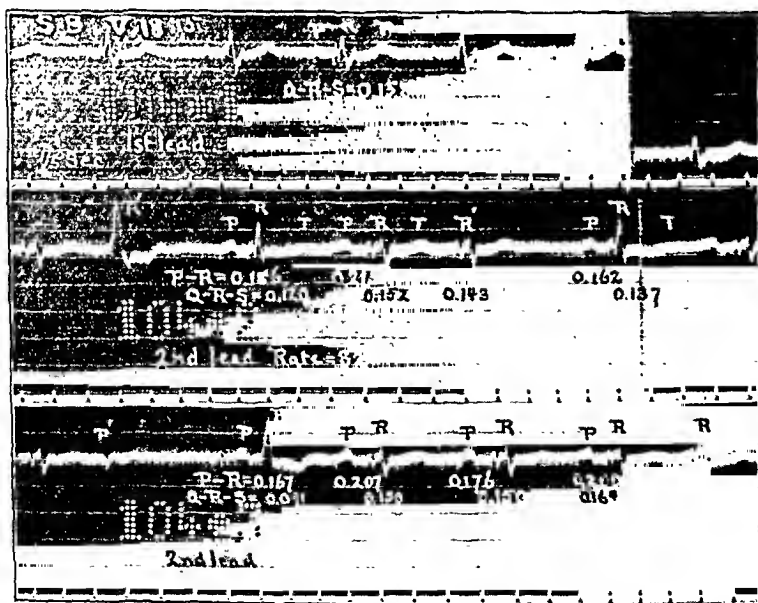


Fig. 3 (Case 2).—Second record, May 18, 1915. The form of ventricular complexes differs from that seen in Figure 2. The Q, R, S time and the P-R time are distinctly prolonged; the form of the ventricular complexes more nearly normal after a prolonged ventricular rest. The patient showed distinct clinical improvement.

ventricular conduction is abnormally delayed, so that the impulse spreads through the ventricles properly only after a prolonged period of ventricular rest.

CASE 3.—A man, 33 years of age, came into the outpatient department complaining of pain in the chest and shortness of breath. The heart dulness extended 5 cm. to the right and 15 cm. to the left of the midsternal line. The heart sounds were distant and blurred, and the heart was beating very rapidly and irregularly. The electrocardiograms (Fig. 4) obtained on this day show a heart rate of 174 per minute. The ventricular complexes occur irregularly and are of unusual forms, while no auricular complexes are visible. The main ascents and descents of the Q, R, S group are gradual, and the time occupied by this group is distinctly prolonged, but difficult to determine accurately. The slight variation of form from beat to beat may be caused by combinations of ventricular complexes with the waves of auricular fibrillation. The patient refused to remain in the hospital. He was put on digitalis and returned in forty-eight hours, after two drams of the tincture had been taken. On this admission there was distinct improvement in symptoms and the heart rate was greatly reduced, varying from 77 to 100 beats per minute. Electrocardiograms (Fig. 5) obtained this day are typical of auricular fibrillation. The arrhythmia is much more marked, and after the longer diastolic pauses, the ventricular complexes have a much more normal form than after the shorter pauses. This is especially noticeable in the first lead, where the abnormal, blunt, low complexes, composed of an R wave with a slow ascent and descent become, after prolonged diastoles, sharp pointed, higher waves resembling closely those usually seen in auricular fibrillation. A study of the various records convinces that this change in form is not caused by combinations of the ventricular complexes with the waves of auricular activity. The fact that this patient died suddenly two days after his second visit, when under a severe emotional strain, suggests that the heart muscle was badly damaged.

The case is one in which the ventricles responded to impulses from the fibrillating auricles at a very rapid rate, and the periods between contractions were not of sufficient duration to allow complete recovery of the intraventricular conduction. The cardiac slowing which resulted from the administration of digitalis caused some improvement in this respect, and resulted in longer ventricular rests, which were followed by ventricular contractions yielding normal or nearly normal complexes.

CASE 4.—A man, aged 59, suffering from syphilis and complete heart block, was under almost continuous observation for a period of nearly two years, during which time numerous electrocardiograms were obtained. During the first six months he had many attacks of unconsciousness and convulsions, with prolonged periods of ventricular inactivity, giving the typical picture of Stokes-Adams syndrome. After March, 1914, these did not occur, and electrocardiograms similar to those shown in Figure 6 were constantly obtained until June 26, 1915. On this day a marked change in the form of the ventricular complexes was noted (Fig. 7). It is seen that a marked change occurs in the form of the Q, R, S group in all leads and the time occupied by the group greatly exceeds the normal. The broad form with the notched top seen in the first lead is especially noteworthy, as it resembles closely the abnormal form seen in the first lead of the first and third cases.

On the day before the record was made the patient had three short "sinking spells," in which he became semiconscious. These spells lasted two

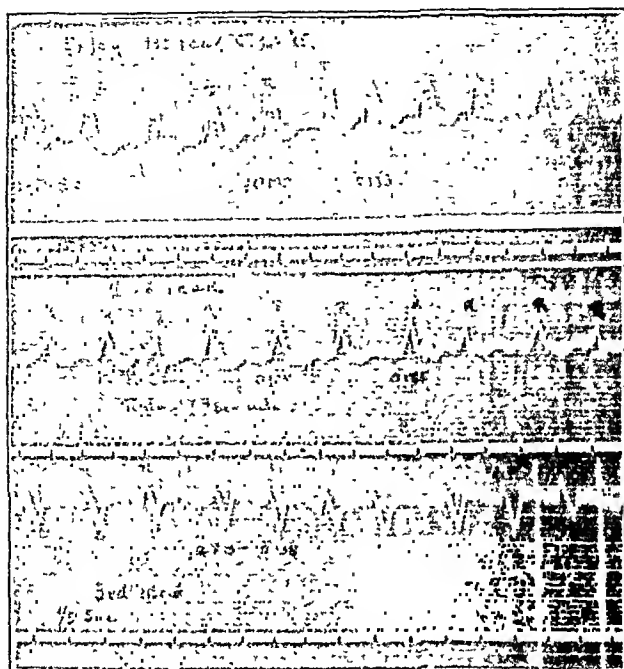


Fig. 4 (Case 3).—May 24, 1915. Auricular fibrillation; very rapid ventricular rate, with markedly deformed ventricular complexes.

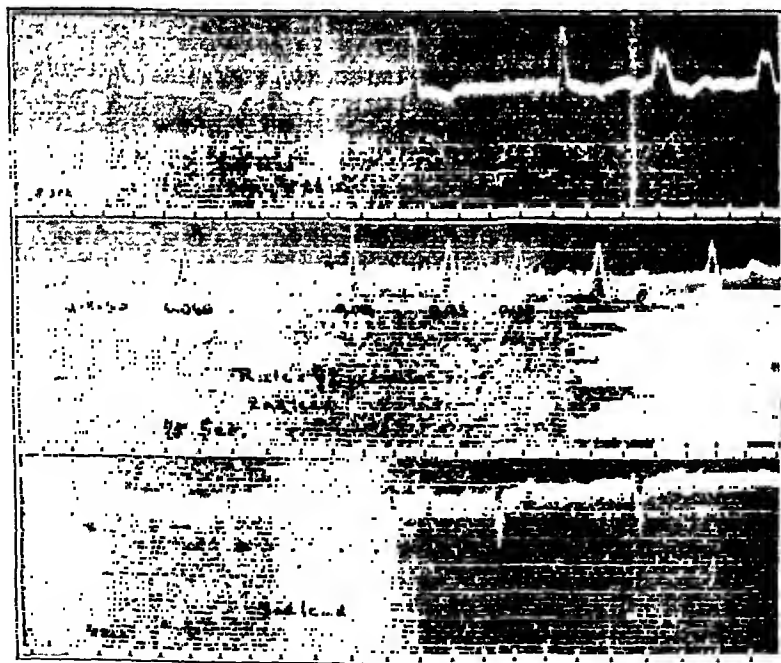


Fig. 5 (Case 3).—May 26, 1915. Auricular fibrillation; after taking tincture of digitalis for forty-eight hours. Striking change in the form of the ventricular complex after ventricular pauses, especially in the first lead.

or three minutes only and came on just as the patient was about to "drop off" to sleep. These spells continued for several days and gradually disappeared. There was no change in the pulse rate at these times of syncope, it remaining between 35 and 43 per minute. During the time when these attacks of syncope occurred the patient was in a critical condition. There was marked cyanosis, dyspnea, Cheyne-Stokes respiration and collections of fluid in the chest, peritoncum and lower extremities. His death was expected hourly, and there seemed to be extreme cardiac insufficiency. But he gradually improved, however, and July 5 he was much better, the cyanosis, dyspnea and edema being less marked. On this date electrocardiograms (Fig. 8) showed another change in form. The following note was made just after the records were taken: "Electrocardiograms taken this afternoon show a very interesting alternation in the form of the Q, R, S group of the ventricular complexes. They are first of the type formerly seen and then of the type which appeared constantly a week or so ago. There is apparently no difference in the effectiveness of the ventricular contractions yielding the varying complexes, as no alternation of the pulse is noted in an examination made directly after the records were obtained, either by palpation of the radial pulse or by auscultation over the brachial artery with the sphygmomanometer applied. The systolic blood pressure is 105 mm. of mercury, the diastolic 45. All beats come through with equal intensity."

At first sight one would be inclined to interpret these changes in form as being caused by contractions set up by impulses arising from two distinct foci, resulting in the passage of the impulses along two different sets of paths. A record obtained with the first lead, however, is evidence for the belief that the impulse of contraction was spreading properly through the ventricles only in alternate beats (Fig. 9). It is seen in this record that a transition form occurs (the third and fifth complexes), suggesting that the spread of the impulse was either not always complete or was not at the same rate through each ventricle. This conception of the variations in the spread of the impulse seems to explain these transition forms of ventricular complexes more satisfactorily than assuming the presence of a shifting focus of stimulus formation.

By July 27, 1915, the patient's condition was greatly improved. He no longer had dizzy spells and was able to be up and about. The electrocardiograms on this date were of the same form as seen previous to the period of marked cardiac insufficiency (Fig. 10).

This case shows a transient but extremely marked change in the form of the ventricular complexes during complete heart block, occurring during a period of great cardiac insufficiency. The abnormally slow rate of the ventricles allows the element of functional fatigue alone to be ruled out. Here the intraventricular conduction was so deranged that the long ventricular pauses at first did not lead to its recovery, while later the intraventricular conduction was apparently normal or partially recovered in alternating beats. Finally the form of the complexes returned to what must be considered the normal for this case, showing that the functional derangement of the ventricles responsible for the change in form was transient.

CASE 5.—A colored woman, aged 30, suffered from a generalized infection with *Streptococcus viridans*, acute endocarditis, embolism, cardiac dilatation and hypertrophy and syphilis. On Oct. 17, 1915, she had moderate dyspnea. The cardiac dulness extended 3.5 cm. to the right and 12 cm. to the left of the midsternal line. The heart rate was 91 per minute, while the systolic blood pressure was 120 mm. of mercury, the diastolic 72. There were no marked

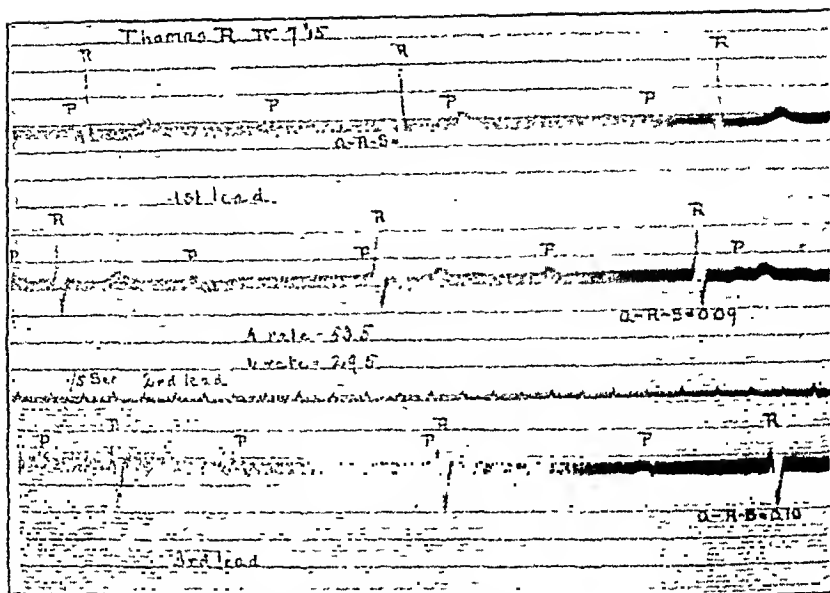


Fig. 6 (Case 4).—April 7, 1915. Complete heart block; the usual type of ventricular complex; normal Q, R, S time.

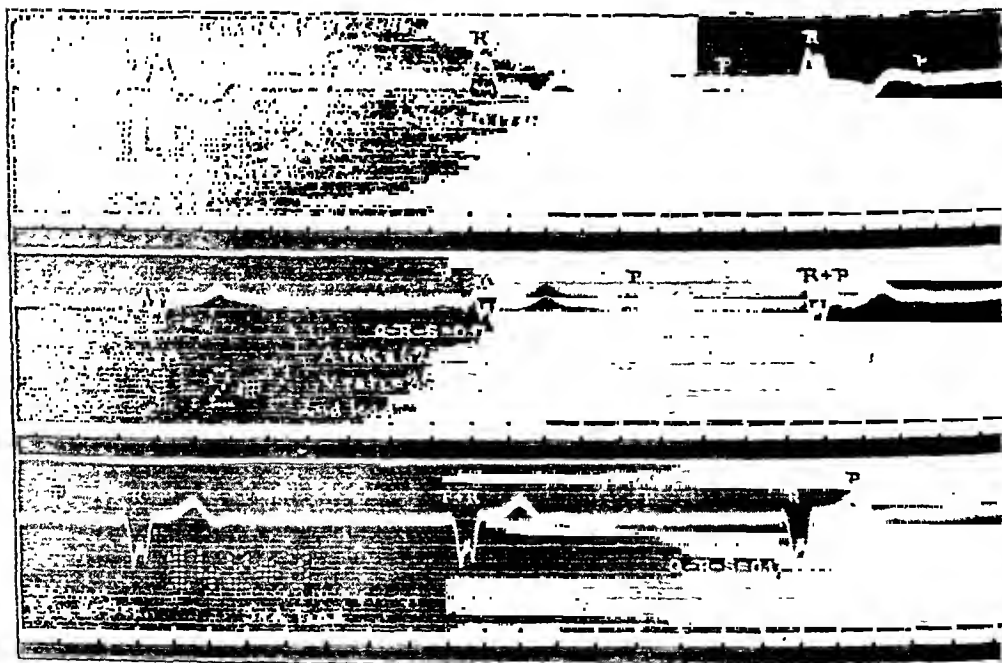


Fig. 7 (Case 4).—June 26, 1915. Striking change in form of the ventricular complex accompanying severe symptoms. Compare with Figure 6.

signs of cardiac insufficiency. The electrocardiograms obtained on this day showed high R waves, with sharp ascents and descents in all leads (Fig. 11).

On Dec. 11, 1915, the patient was very ill and showed definite signs of decompensation. The systolic blood pressure had fallen 27 mm. of mercury, while the diastolic pressure was unchanged. The heart rate was 110. The outline of cardiac dullness was unchanged. Electrocardiograms (Fig. 12) show a distinct change in form of the ventricular complexes, the R waves being much less high, and the ascent and descent, especially in the first lead, being slow. The Q, R, S time is not, however, definitely changed.

In this case well-defined changes in the ventricular complexes occurred synchronously with distinct decrease in cardiac efficiency. The form of the complexes resembles sufficiently those accompanying definite functional depression in the previous cases to suggest that the change which occurred during failure of the cardiac efficiency is the result of the cardiac failure and indicates presumably derangement of the intraventricular conduction.

CASE 6 is an example of change in form of the ventricular complex which occurred synchronously with a marked improvement in symptoms and apparently because of functional improvement of the ventricles. The patient was a woman of 24 who suffered from aortic and mitral insufficiency and who showed at times alternation of the heart beat. On June 17, 1915, when the record shown in Figure 13 was obtained, there was dyspnea while at rest in bed and other signs of cardiac decompensation. The electrocardiogram shows a slightly slowed ascent and descent in the R waves, and in Lead I the blunt, split-topped form is seen, which suggests that seen in some of the previous cases.

These abnormalities are less marked, and almost absent in records obtained on May 24, 1916 (Fig. 14), when the patient was no longer in the hospital, but returned merely for observation. On this day there was slight dyspnea after walking to the heart station, but no other symptoms suggesting cardiac insufficiency.

The change in form in the ventricular complexes which accompanied marked improvement of the cardiac efficiency seems to indicate that the abnormalities of the complexes observed during definite decompensation were dependent on the cardiac insufficiency. The fact that in this case alternation of the heart beat was not accompanied by alternation in the form of the ventricular complexes is evidence in favor of the belief that the abnormalities seen in Figure 13 were not caused by changes in muscular contractions as such, and makes it appear more likely that they resulted from defective conduction of the impulses through the ventricular musculature.

CASE 7 is included as one of marked cardiac decompensation, which showed abnormal ventricular complexes similar to those seen in the previous case. The electrocardiogram (Fig. 15) was obtained from a man with aortic insufficiency of syphilitic origin, whose heart was evidently much dilated. Here again the gradual ascent and descent of the limbs of the R waves are seen, especially in the second lead. The same blunt, notched wave is seen in the first lead, while the third lead complex is distinctly peculiar. The patient died suddenly a few days after the record was obtained, following the intravenous administration of strophanthin. It seemed not unlikely that ventricular fibrillation resulted from the administration of the drug.

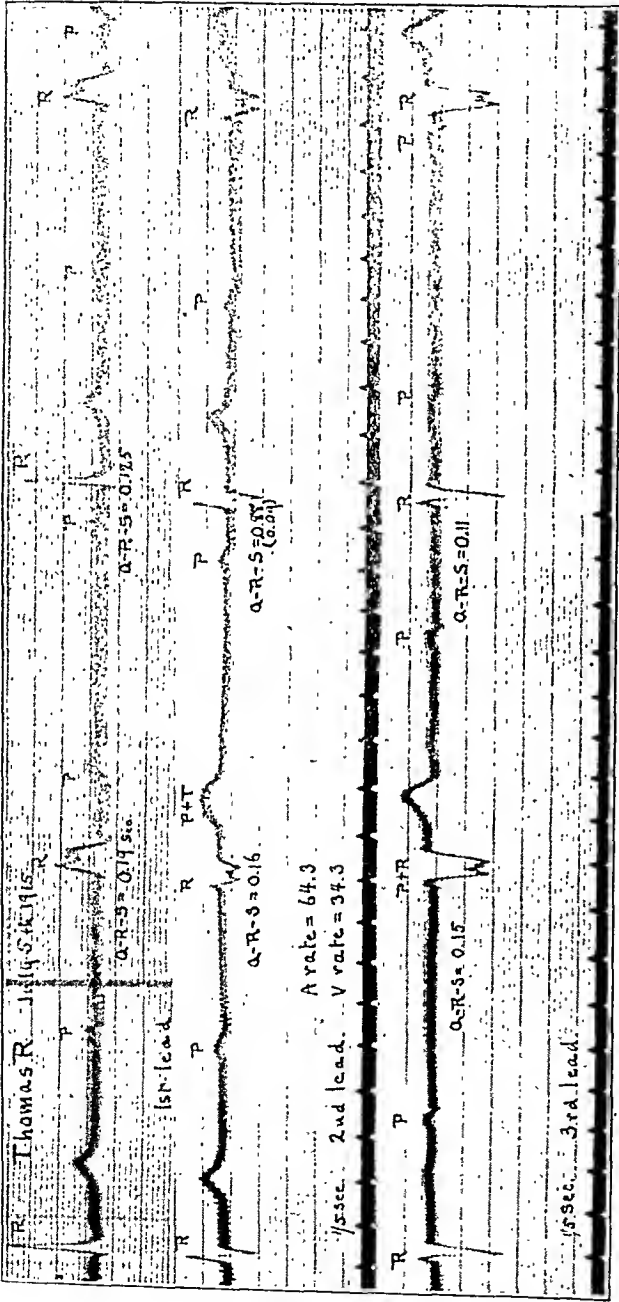


Fig. 8 (Case 4).—July 5, 1915. The form of the complexes alternate; first the usual form and then the form that appeared nine days previously.



Fig. 9 (Case 4).—July 5, 1915. Transition between the old and the new forms of the first lead complexes.

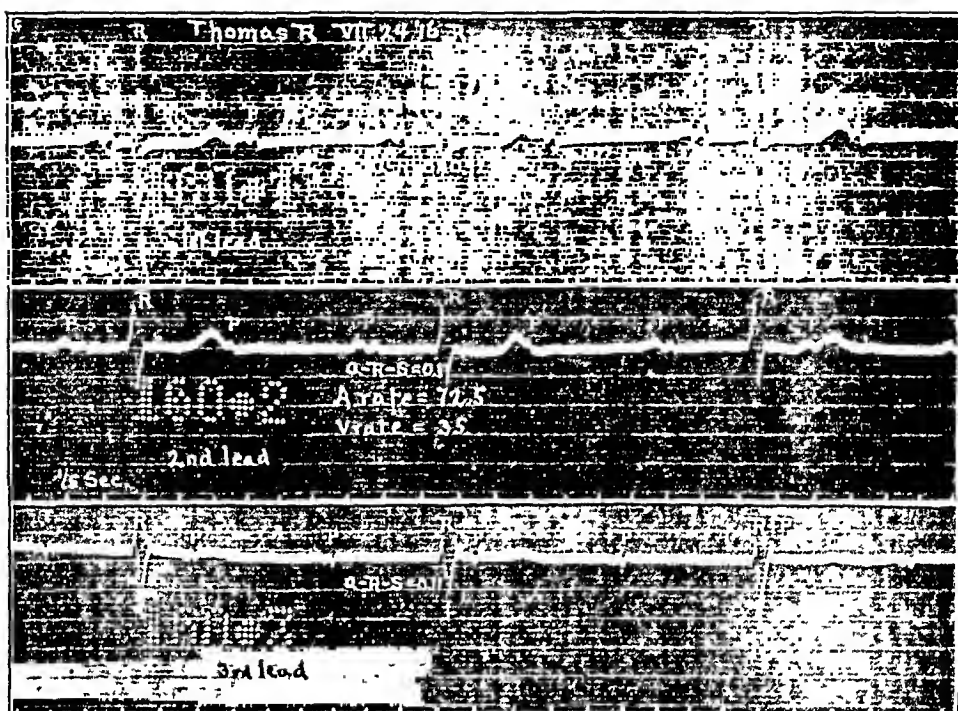


Fig. 10 (Case 4).—July 24, 1915. The form of the ventricular complexes is constantly that seen before the marked change occurred. No further change occurred.

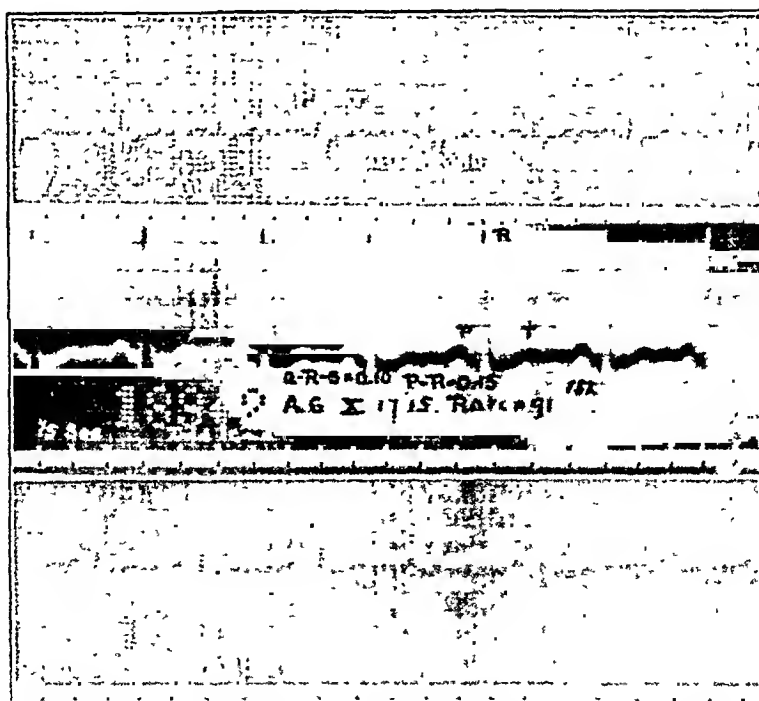


Fig. 11 (Case 5).—Oct. 17, 1915. Cardiac efficiency but slightly impaired.

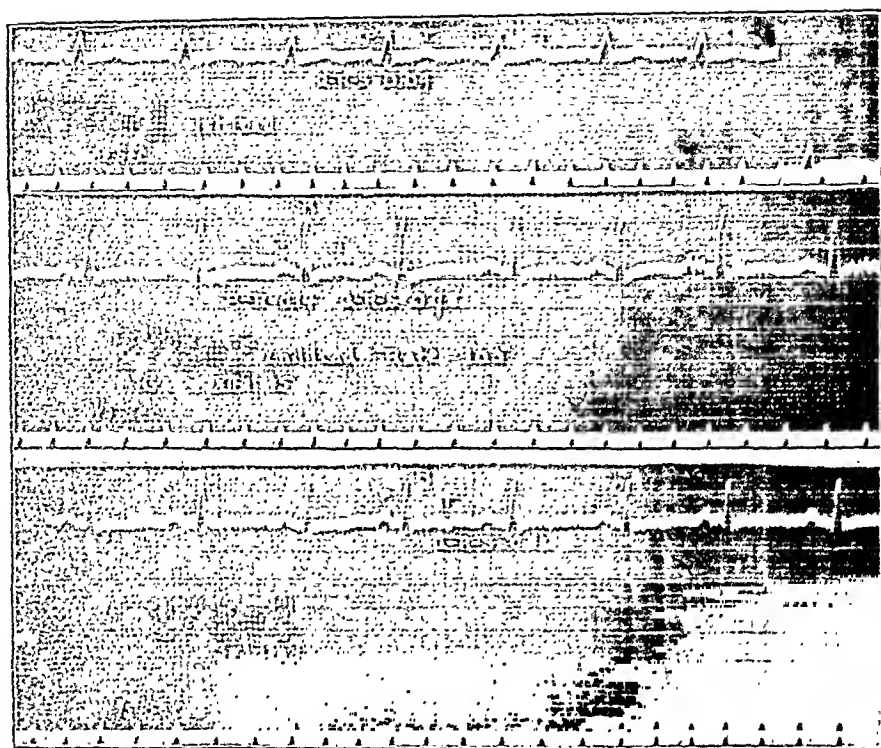


Fig. 12 (Case 5).—Dec. 11, 1915. Cardiac efficiency much impaired.

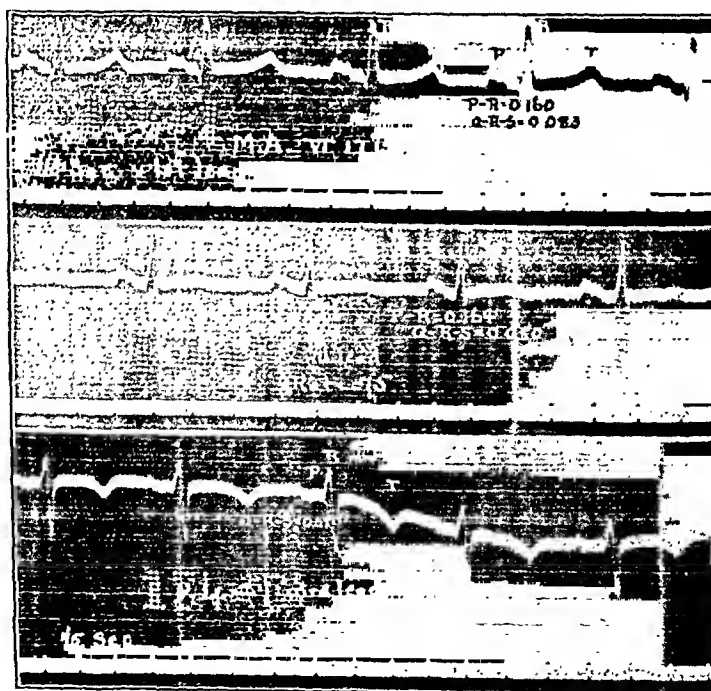


Fig. 13 (Case 6).—June 17, 1915. Marked signs of cardiac decompensation.

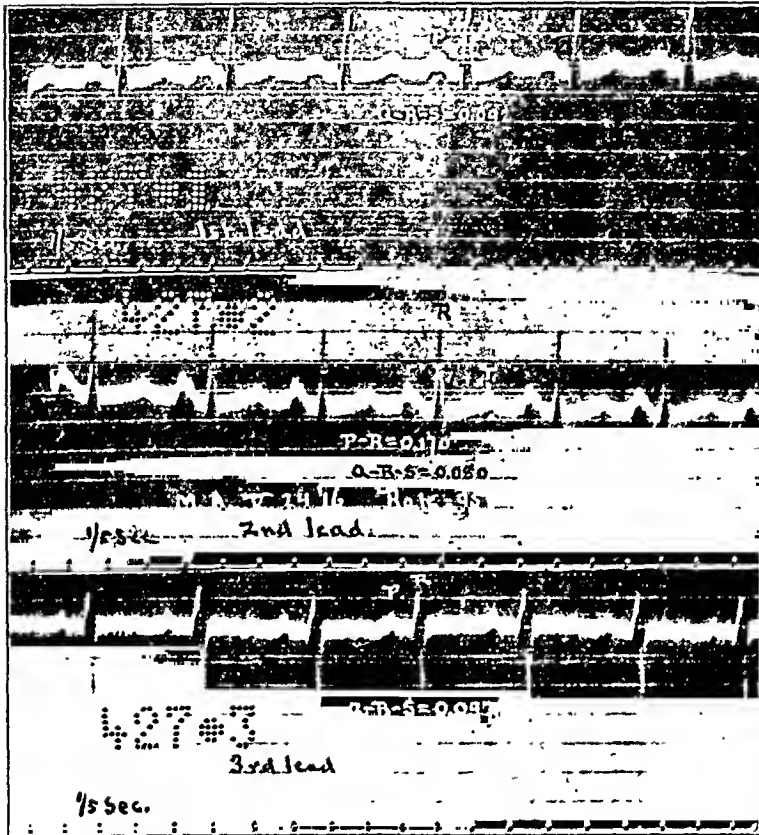


Fig. 14 (Case 6).—May 24, 1916. Patient much improved; cardiac decompensation slight.

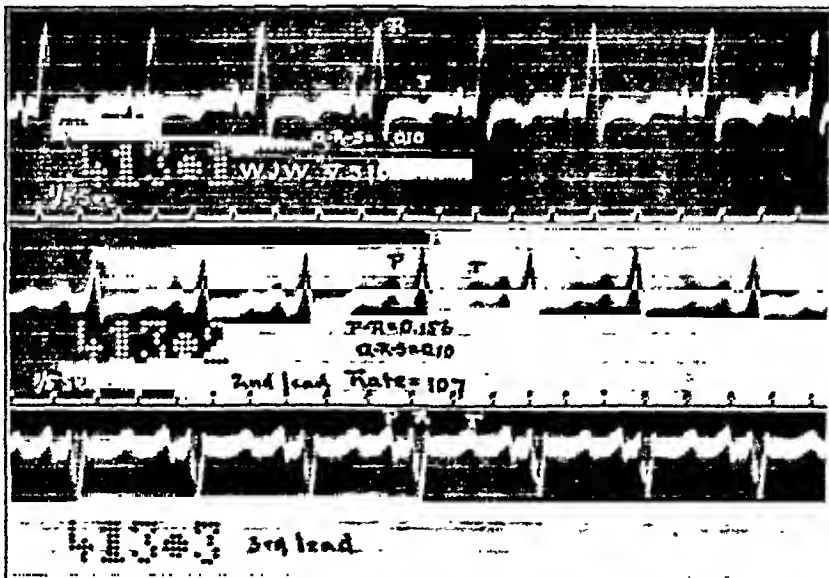


Fig. 15 (Case 7).—May 3, 1916. Patient showed signs of extreme cardiac decompensation.

COMMENT

The idea that changes in form of the ventricular complexes may depend on faulty conduction through the ventricles of impulses descending from the auricles was first suggested by Lewis.⁹ He based his hypothesis on records obtained under experimental conditions, as well as on electrocardiograms from clinical material, and developed his idea further in a second paper.⁸ He points out the association of prolonged auriculoventricular conduction with the so-called aberrant contractions, and suggests that abnormal complexes may depend on damage affecting special branches of the intraventricular conducting system. Under such conditions the impulse is at one time transmitted through the whole arborization, while at other times it passes into the arborization, but fails to course along certain given channels.

Hart¹⁰ has also recognized derangement of intraventricular conduction as a cause of contractions yielding abnormal ventricular complexes. He shows records in which the Q, R, S group of the complex is deformed in a manner somewhat similar to deformities described in this paper and he believes that the abnormalities are caused by damage to the musculature, so that the passage of impulses is interfered with in all parts of the conducting system.

The occurrence of varying ventricular complexes in cases of complete heart block has been reported by Cohn¹¹ and by Oppenheimer and Williams.¹² These cases have been interpreted as examples of either a shifting focus of stimulus formation within the ventricles or as interference with intraventricular conduction. The changes in form of the ventricular complexes of the case reported here are considered as dependent on interference of ventricular conduction.

The purpose of this paper is not primarily to record a series of cases showing derangement of intraventricular conduction. This change in function is discussed only as affording an explanation of the changes in form of the ventricular complexes which have been observed. The object of the paper is to point out certain abnormalities occurring in electrocardiographic curves which apparently accompany functional deficiency of the ventricles. This is done with the hope that the electrocardiographic method may sometimes prove of value in determining

9. Lewis: *Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature*, Heart, 1910, ii, 23.

10. Hart: *Paroxysmal Tachycardia*, Heart, 1912, iv, 128.

11. Cohn: *A Case of Transient Complete Auriculoventricular Dissociation, Showing Constantly Varying Ventricular Complexes*, Heart, 1913, v, 5.

12. Oppenheimer and Williams: *Prolonged Complete Heart Block, Without Lesion of the Bundle of His and with Frequent Changes in the Idioventricular Electrical Complexes*, Proc. Soc. Exper. Biol. and Med., 1913, x, 86.

changes in the functional capacity of the ventricular musculature, perhaps the most important and one of the most obscure problems involved in the study of the heart.

Only a much wider experience and a collection of many such cases as those exemplified in this paper can determine the value of these observations from the purely clinical point of view.

SUMMARY

A series of cases is reported which yielded electrocardiograms showing abnormal ventricular complexes. These abnormalities consist in changes in the initial portion of the complexes, the Q, R, S group, and differ from those yielded by contractions caused by ectopic stimuli and from those changes which occur with bundle-branch block.

These abnormalities are apparently dependent on derangement of the intraventricular conduction, which prevents the passage of the excitation wave either along the usual paths or at the usual rate throughout the ventricles.

The normal spread of the impulse is hindered because the impulse reaches the ventricles before the conducting system has recovered from the preceding contraction, and the records indicate in some cases that this derangement disappears with prolonged ventricular rest.

These observations are taken as evidence for the belief that in cases in which the ventricular complexes constantly show certain abnormal forms, there are functional changes in the heart which prevent the normal recovery of intraventricular conduction during diastole. It is shown that changes in form of the ventricular portions of the electrocardiogram may occur synchronously with functional changes in the heart, and evidence is offered for the belief that certain abnormalities in the form of the electrocardiogram indicate functional derangement of the ventricles.

A STUDY OF LOW BLOOD PRESSURES NOT ASSOCIATED WITH TRAUMA OR HEMORRHAGE*

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CHICAGO

In the course of studies on anaphylactic shock in the dog it was found that during the period of low blood pressure the pressor effect of nicotin may be greatly augmented at a time when epinephrin produces little or no result.¹ Exactly similar reactions were found in peptone shock. Low blood pressures from hemorrhage are sharply distinguished from the above by the fact that in them, while the effect of nicotin may be exaggerated, that of epinephrin remains unchanged, as shown by Hoskins, Rowley and Rosser.² It seems not improbable, therefore, that the mechanism of these phenomena may be different.

It was suggested in connection with the study of anaphylactic shock that the augmented action of nicotin in that condition was due largely if not entirely to its effect on respiration. Further observations on this point are here reported, partly because they may have some bearing on the question of the effect of respiration on blood pressure, and partly because they may find practical application in the treatment of certain forms of shock.

The technic employed was that used in the previous study, namely, that described by Hoskins and Wheelon.³ The animals were anesthetized with ether. A canula in the carotid or femoral artery was connected with a mercury manometer. A second canula in the femoral vein was connected with a buret containing physiologic salt solution, with a pinch-cock on the rubber connection immediately above the canula. Standard doses of nicotin (1 c.c. of 1 to 4,000 solution) and of epinephrin (1 c.c. of 1 to 20,000 solution) were administered by inserting the needle of the syringe into the rubber tube immediately above the pinch-cock. After being injected into the tube the drug was quickly and completely washed into the vein with from 6 to 8 c.c. of salt solution. The normal reactions of the animal to standard doses of nicotin and epinephrin were first determined. Known amounts of Witte's peptone in solution, or, in the case of sensitized animals, of normal horse serum, were then injected. After the blood pressure

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* From the Department of Pathology of Northwestern University Medical School.

1. Simonds, J. P.: *Jour. Infect. Dis.*, 1916, xix, 746.

2. Hoskins, Rowley and Rosser: *THE ARCHIVES INT. MED.*, 1916, xvi, 456.

3. Hoskins and Wheelon: *Am. Jour. Physiol.*, 1914, xxxiv, 81.

had reached its lowest level the injections of epinephrin and nicotin were repeated at frequent intervals.

The results are shown graphically in Figures 1 to 4. In Figure 1 sections of the blood pressure tracing of Dog *A14-p* are shown. This animal was given 1 c.c. of normal horse serum subcutaneously on Feb. 3, 1915. On February 24 the normal reactions to epinephrin and nicotin were recorded, and 5 c.c. of normal horse serum were injected intravenously. There was no fall in blood pressure during the following twenty minutes and 2 gm. of Witte's peptone in salt solution were given intravenously. The blood pressure fell promptly, but during the period of fall the animal made several violent respiratory efforts, at which time the decline became less steep and even almost ceased for a few seconds. The first injections of nicotin and epinephrin given two and three minutes, respectively, after the administration of the peptone produced no effect either on respiration or blood pressure. (The tracing for epinephrin is not shown.) An injection of nicotin given six minutes after the peptone caused some dyspnea and a rise in pressure greater than the normal for that animal (Fig. 1, 5). One minute later epinephrin caused only a slight rise in pressure (Fig. 1, 6). Two minutes afterward, that is, nine minutes after the injection of the peptone, nicotin gave a markedly exaggerated reaction, the pressure reached almost normal and did not fall again (Fig. 1, 7). It may be noted in passing that the effect of dyspnea in increasing the amplitude of the swing of the manometer is not so evident in these conditions of low blood pressure as when the pressure is at its normal level and the heart filling and emptying itself properly at each beat. This is shown especially well in Figure 4.

Small openings were made between the ribs into the pleural cavities in Dog *P C O 1* (Fig. 2) and artificial respiration was employed. The normal reactions to epinephrin and nicotin were then recorded. This animal was very sensitive to epinephrin. Two grams of Witte's peptone dissolved in 20 c.c. of salt solution were washed into the femoral vein with 60 c.c. of salt solution. The volume rise was quite marked, but was followed by an immediate fall in blood pressure. During the following thirty minutes none of the frequently repeated injections of nicotin produced anything like the normal response. In most instances the only perceptible result was the slight transient rise that was due to the volume of fluid with which the drug was washed into the vein. The effect of epinephrin, to which this animal was especially sensitive, was evident from the first injection. The last injection of this substance caused a rise in pressure equal to about one-half the normal response for this animal, but it brought the pressure back to approximately its original level, where it remained.

In Dog *P C O 2* (Fig. 3) the normal reactions to nicotin and

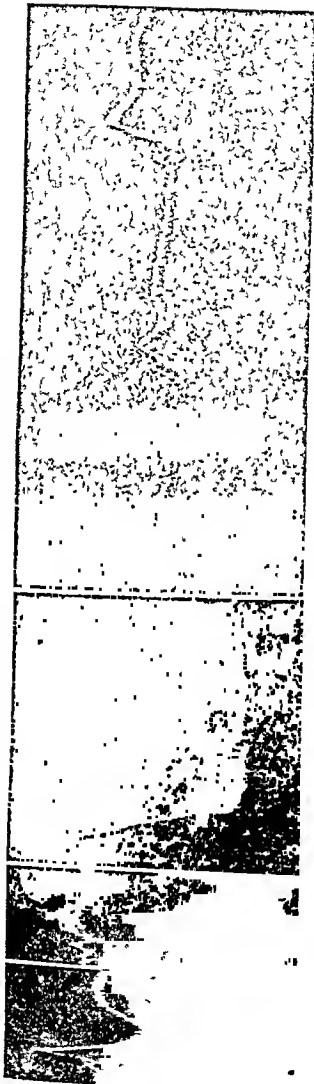


Fig. 1.—Dog A 14p: On February 3, 1 c.c. normal horse serum was injected subcutaneously, and on February 24, 5 c.c. were injected. No fall in blood pressure occurred. Twenty minutes later 2 gm. of Witte's peptone dissolved in salt solution were given intravenously. Division 1 shows normal reaction to epinephrin; 2 shows normal reaction to nicotine; in 3 there were given 2 gm. of peptone intravenously at 11:22 a. m.; in 4 nicotine was injected at 11:24 a. m., with no reaction. There was no reaction to epinephrin injected one minute later (not shown on tracing). At 5 nicotine was injected (11:28 a. m.). There was no dyspnea and an augmented rise in blood pressure, which remained higher than before. At 6 epinephrin was injected (11:29 a. m.). There was decreased reaction to less than one-half the normal. At 7 nicotine was injected (11:31 a. m.). There was dyspnea and exaggerated rise in pressure, which was subsequently sustained at this level.

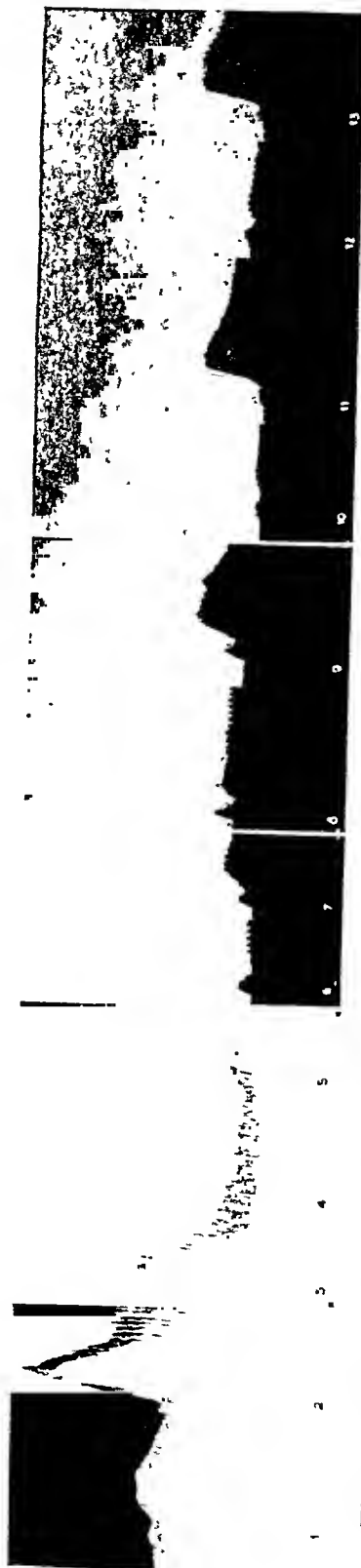


Fig. 2.—Dog P C O 1: To determine the effect of opening the chest and the use of artificial respiration on the reaction to nicotine small openings were made between the ribs into both pleural cavities at 9:35 a. m. At 1 is shown the normal reaction to nicotine with the chest open; at 2 is shown the normal reaction to epinephrin with the chest open. This animal was very sensitive to epinephrin. There were given at 3 Witte's peptone, 2 gm., in salt solution, injected at 9:43 a. m. There was marked volume rise with sharp fall in pressure. At 4 nicotine was injected at 9:44 a. m., and at 5 epinephrin was injected at 9:45 a. m. Again at 6 nicotine was injected with 12 c.c. salt solution at 9:50 a. m.; at 7 epinephrin was injected at 9:52 a. m.; at 8 nicotine was injected at 9:59 a. m.; at 9 epinephrin was injected at 10:01 a. m.; at 10 nicotine was injected at 10:13 a. m.; at 11 epinephrin was injected at 10:15 a. m.; at 12 nicotine was injected at 10:17 a. m.; and at 13 epinephrin was injected at 10:20 a. m.

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Fig. 3.—Dog P C O 2: This experiment was undertaken to determine the effect of opening the chest on the reaction to nicotine. At 1 is shown the normal reaction to nicotine before opening the chest, and at 2 the normal reaction to epinephrin before opening the chest. Small openings made between the ribs into both pleural cavities at 9:35 a. m. At 3 is shown the reaction to nicotine after opening the chest, and at 4 the reaction to epinephrin after opening the chest. At 5 were given 3 gm. Witte's peptone in salt solution at 9:42 a. m. At 6 nicotine was injected at 9:43 a. m.; at 7 epinephrin was injected at 9:44 a. m.; at 8 epinephrin was injected at 9:58 a. m.; at 9 nicotine was injected at 10:04 a. m., with volume rise only. At 10 epinephrin was injected at 10:10 a. m.; at 11 nicotine was injected at 10:12 a. m.; at 12 nicotine was injected at 10:26 a. m., and at 13 epinephrin was injected at 10:27 a. m. The openings in the chest wall were closed with clamps at 10:30 a. m., and the animal breathed spontaneously. At 15 epinephrin was injected at 10:33 a. m., and at 16 nicotine was injected at 10:34 a. m.



Fig. 4.—Dog P R 1: This experiment shows the effect of violent respiratory effort on blood pressure in peptone shock. The upper tracing shows the respiration, the lower one, blood pressure. (While taking this tracing, at a point on the chart between a and b the rubber tube connecting the tracheal cannula with the Marey tambour became kinked and only a straight line was registered, although the animal was still in a condition of dyspnea. An attempt was made without much success, to trace this in afterward.) At 1 is shown the normal reaction to nicotine, and at 2 the normal reaction to epinephrin. At 3 there were given 2 gm. Witte's peptone in salt solution, injected intravenously, at 10:29 a. m. At 4 nicotine was injected at 10:30 a. m.; at 5 epinephrin was injected at 10:32 a. m.; at 6 nicotine was injected at 11:04 a. m.; at 7 nicotine was injected at 11:36 a. m., and at 9 nicotine was injected at 11:56 a. m.

epinephrin were obtained before (Fig. 3, 1 and 2) and after (Fig. 3, 3 and 4) opening the chest and using artificial respiration. The results show that the process of opening into the pleural cavities and the use of artificial respiration did not materially affect the normal reactions to these drugs. Three grams of Witte's peptone in 30 c.c. of salt solution were then injected intravenously, which caused a prompt and marked fall in blood pressure. The first doses of epinephrin and nicotin caused no perceptible rise. It was only after sixteen minutes had elapsed that epinephrin began to give a reaction (Fig. 3, 8). After twenty-two minutes nicotin still caused no response (Fig. 3, 9). After forty-four and forty-five minutes, respectively, both nicotin and epinephrin gave subnormal reactions, the latter being proportionally stronger than the former. At no time did a standard dose of nicotin cause its normal response.

Figure 4 shows the respiration curve, taken with a Marey tambour, and the blood pressure curve of a dog which was given 2 gm. of Witte's peptone. The effect of dyspnea on the action of nicotin in low blood pressures of this type is well shown. Figure 4, 8 shows the effect of a standard dose of nicotin, given nearly an hour after the onset of shock, which did not, for some reason, affect the respiration. Just why similar doses of nicotin should act on respiration differently at different times in the same animal cannot now be stated. It may have been due to variations in the depth of anesthesia, although there is no particular reason why, in this instance, the degree of anesthesia should have varied greatly. Figure 4, 6 and 8, shows the marked effect of nicotin when dyspnea is produced.

The results of these observations may be stated briefly thus: In conditions of low blood pressure due to anaphylactic shock and peptone poisoning the exaggerated reaction to nicotin frequently observed is associated with violent respiratory effort. Opening the chest and employment of artificial respiration effectively prevent this result, although they do not materially affect the reaction to nicotin before the condition of shock has been induced. It is believed, therefore, that this augmented effect in these two conditions is due to its action on respiration rather than any action on the vasomotor apparatus itself.

Swale Vincent⁴ has shown that under conditions of normal blood pressure violent dyspnea has a distinctly depressor effect. Henderson and Barringer⁵ believe that "the utmost assistance which respiration can afford to the circulation is to maintain a venous pressure sufficient to distend the right ventricle as rapidly as it relaxes and as fully as the duration of the diastole allows." The "critical venous pressure"

4. Vincent, Swale: *Quart. Jour. Physiol.*, 1915, ix, 45.

5. Henderson and Barringer: *Am. Jour. Physiol.*, 1912-1913, xxxi, 399.

necessary to accomplish this is "not more than 50 mm. of saline."⁶ The negative pressure maintained around the heart by the elasticity of the lungs, according to these observers, is approximately equal to the critical venous pressure. Lewis⁷ found that in man "a deep intercostal inspiration, which is not prolonged, yields a pure fall in blood pressure; a deep diaphragmatic inspiration, which is not prolonged, gives a pure rise in blood pressure. The rise in blood pressure in abdominal breathing is due to the raised intra-abdominal pressure."

It appears to be generally accepted, therefore, that in the normal animal increased respiration produces little if any rise in blood pressure and may even cause a fall. This is true for several reasons: First, the veins are uniformly filled, venous pressure is normal, and as Henderson and Barringer⁸ have pointed out, any suction that might be produced by respiratory effort cannot be transmitted through these collapsible tubes to any distance outside the thorax. Second, with the heart normally filling and emptying itself at each beat, the percentage of blood that could be added by respiratory effort would be small. Third, there is no reservoir of accumulated blood comparatively near the heart on which suction can be exerted.

In anaphylactic and peptone shock, however, an entirely different condition exists. In the first place, the venous pressure is low and the heart is not filling normally. There is room, therefore, for a considerable increase in the percentage of blood that could be added to the heart during each diastole if a source of supply were available. Such a supply is at hand in the overfilled venous trunks and in the veins of the liver and splanchnic area. Even in the process of collapsing under the influence of suction such turgid vessels would deliver to the heart a larger volume of blood than normally filled vessels could do. Furthermore, the veins of the liver are not readily collapsible, and Edmunds⁸ has shown that in anaphylactic shock there is a very marked increase in the volume of the liver due to the accumulation of blood in that organ. Suction exerted on the dilated hepatic veins by increased respiratory effort would not cause their collapse, but would draw from them a much greater amount of blood than could thus be extracted from the normal liver. The increased intra-abdominal pressure in dyspnea would help to keep the dilated veins of the liver filled by pressing into them blood from the veins of the splanchnic area.

Low blood pressures due to hemorrhage and to circulatory shock of the type under discussion are, as shown by Henderson,⁹ identical

6. Henderson and Barringer: *Am. Jour. Physiol.*, 1912-1913, xxxi, 352.

7. Lewis: *Jour. Physiol.*, 1908, xxxvii, 233.

8. Edmunds: *Ztschr. f. Immunitätsforsch. u. exper. Therap., Original*, 1914, xxii, 181.

9. Henderson: *Am. Jour. Physiol.*, 1910, xxvii, 152.

in mechanism, in that in both the venous supply to the right side of the heart is the critical factor. In both the venous pressure is low and too little blood reaches the right side of the heart. But there is this sharp difference, that in the circulatory shock there is a large reservoir of stagnant blood in the veins of the liver and splanchnic region, while after hemorrhage no such reservoir is present. This distinction is important from a therapeutic standpoint and in the interpretation of the results of the injection of nicotin reported above.

In low blood pressure from hemorrhage, as shown by Hoskins, Rowley and Rosser¹⁰ there is an increased irritability of the vasomotor center as manifested by the augmented reaction to nicotin. This phenomenon, in this case, is undoubtedly chiefly if not wholly of central origin. The mechanical effect of increased respiratory effort under such conditions would be slight because of the absence of any reservoir of accumulated blood on which suction could be exerted; and because the veins, being already underfilled, would collapse all the more readily and suction could not be transmitted through them even to the slight extent to which it is transmitted through normal veins.

In the case of low blood pressure from anaphylactic and peptone shock, however, an entirely different condition exists. In the first place, the greatly reduced response to injections of nicotin that are observed when, for any reason, dyspnea is not produced, is suggestive of a condition of reduced irritability of the vasomotor center (Fig. 4, 7). When, however, dyspnea is produced, suction is exerted on the overfilled veins of the liver and sufficient blood is drawn into the heart to cause an exaggerated rise in pressure.

In human patients in the treatment of shock associated with low blood pressure not due to hemorrhage, Pearce and Eisenbrey¹¹ recommend the use of epinephrin and intravenous injections of salt solutions. Neither of these procedures was effective in my animals, although it is quite possible that they might be more so in human cases. In my animals the paralysis of the nerve endings in the vessel walls was too great for the epinephrin to cause a rise in pressure. Intravenous injections of comparatively large quantities of salt solution yielded relatively slight increase in pressure. The added fluid apparently went chiefly to increase the dilatation of the splanchnic vessels. For example, a dog in peptone shock with a blood pressure of 32 mm. of mercury received, during a period of two minutes, 225 c.c. of salt solution at 40 C. As a result of this treatment, the highest pressure reached was 48 mm. of mercury, and by the end of three minutes

10. Hoskins, Rowley and Rosser: *THE ARCHIVES INT. MED.*, 1915, xvi, 456.

11. Pearce and Eisenbrey: *THE ARCHIVES INT. MED.*, 1910, vi, 218.

from the beginning of the injection, the pressure had sunk to 40 mm., above which it did not again rise, and the animal ultimately succumbed.

In such cases the injection of nicotin, on the other hand, by causing increased respiratory effort, led to rise in blood pressure and frequently saved the life of the animal, even when death seemed imminent.¹² In the treatment of this type of circulatory shock in man it is possible that any measure which will excite more or less dyspnea (not necessarily nicotin) would raise blood pressure and improve the condition of the patient. Perhaps, when possible, voluntary deep and rapid breathing on the part of the patient at frequent intervals might work good results. It might at least help to prevent a serious loss of tonus from a too long-continued overdilatation of the vessels concerned.

SUMMARY

The condition of low blood pressure due to anaphylactic shock and peptone poisoning is characterized by absence or marked diminution of the reaction to epinephrin, and an exaggerated response to nicotin. It would appear that there is a condition of reduced irritability on the part of the vasomotor center, and that the increased reaction to nicotin is largely mechanical, resulting from the effect of the drug on respiration. The dyspnea so produced causes suction on the overfilled non-collapsible veins of the liver and brings sufficient blood to the under-filled right side of the heart and ultimately to the systemic vessels, in which the pressure is raised. It is suggested that in cases of shock in man, associated with low blood pressure not due to hemorrhage, the artificial production of dyspnea or the voluntary increase of the rate and depth of respiration by the patient may lead to improvement.

12. Simonds, J. P.: Footnote 1, Chart 2.

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